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Review

Amyloid imaging: Past, present and future perspectives

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by the gradual onset of dementia. The pathological hallmarks of the disease are Aβ amyloid plaques, and tau neurofibrillary tangles, along dendritic and synaptic loss and reactive gliosis.

Functional and molecular neuroimaging techniques such as positron emission tomography (PET) using functional and molecular tracers, in conjuction with other Aβ and tau biomarkers in CSF, are proving valuable in the differential diagnosis of AD, as well as in establishing disease prognosis. With the advent of new therapeutic strategies, there has been an increasing application of these techniques for the determination of Aβ burden in vivo in the patient selection, evaluation of target engagement and assessment of the efficacy of therapeutic approaches aimed at reducing Aβ in the brain.

Contents

1. Introduction

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is an irreversible, progressive neurodegenerative disorder clinically characterized by memory loss and cognitive decline (Khachaturian, 1985), leading invariably to death, usually within 7–10 years after diagnosis. Age is the dominant risk factor in AD. The progressive nature of neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage (Isacson et al., 2002) in cortical areas of the brain essential for memory and higher mental functions, eventually affecting activities of daily living.

From a neuropathological perspective, the typical macroscopic picture of an AD brain shows gross cortical atrophy. Microscopically, there is widespread cellular degeneration and neuronal loss that affects primarily the outer three layers of the cerebral cortex. These changes are accompanied by reactive gliosis, diffuse synaptic and neuronal loss, and by the presence of the pathological hallmarks of the disease, intracellular neurofibrillary tangles (NFT) and extracellular amyloid plaques. (Jellinger, 1990; Masters, 2005; Masters and Beyreuther, 2005) Neurofibrillary tangles are intraneuronal bundles of paired helical filaments constituted by an abnormally phosphorylated form of the tau protein (Jellinger and Bancher, 1998; Michaelis et al., 2002). Plaques consist of extracellular aggregates of a 4 kDa self-aggregating, 39–43 amino acid metallopeptide, amyloid β-peptide (Aβ) (Masters et al., 1985),

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derived from the proteolytic cleavage of the amyloid precursor protein (APP) by β and γ-secretases. (Cappai and White, 1999).

For the last 20 years the clinical diagnosis of AD was based on progressive impairment of memory and decline in at least one other cognitive domain, and by excluding other diseases that might also present with dementia such as frontotemporal dementia (FTD), dementia with Lewy-bodies (DLB), stroke, brain tumor, normal pressure hydrocephalus or depression. (Cummings et al., 1998; Larson et al., 1996) In other words, dementia. (McKhann et al., 1984). Diagnostic accuracy for AD usually depends on the disease stage and can exceed 90% in academic settings in mid or late stages (Rasmusson et al., 1996). The new criteria for the diagnosis of AD introduces imaging and fluid biomarker information and does not require the presence of dementia (Dubois et al., 2010, 2007). A variable period of up to five years of prodromal decline in cognition characterized by a relatively isolated impairment in memory, known as Mild Cognitive Impairment (MCI), usually precedes the formal diagnosis of AD. (Petersen, 2000; Petersen et al., 1999, 2001) About 40–60% of carefully characterized subjects with MCI will subsequently progress to meet criteria for AD over a 3–4-year period (Petersen, 2000; Petersen et al., 1995, 1999).

Despite all the tremendous corpus of knowledge of genetics, epidemiology, risk factors, and neuropathological mechanisms, there is still no cure for AD.

2. Molecular neuroimaging in AD

2.1. Functional neuroimaging

The insight into the molecular mechanism of AD pathogenesis opened new avenues for the successful development of new neuroimaging approaches. (Selkoe, 2000) Modern functional neuroimaging techniques such as positron emission tomography (PET), tend to be more sensitive than structural imaging modalities, identifying subtle pathophysiologic changes in the brain, before structural changes are present (Bobinski et al., 1999; de Leon et al., 1997; De Toledo-Morrell et al., 2000; Dickerson et al., 2001; Juottonen et al., 1998; Killiany et al., 2000; Xu et al., 2000), therefore possessing greater potential for accurate and early diagnosis, monitoring disease progression, and better treatment follow-up (Silverman and Phelps, 2001; Villemagne et al., 2005). PET is a sensitive molecular imaging technique that allows in vivo quantification of radiotracer concentrations in the picomolar range, where either the radiotracer bears the same biochemical structure, is an analog or a substrate of the chemical process being evaluated, allowing the in vivo assessment of the molecular process at their sites of action, (Phelps, 2000) permitting detection of disease processes at asymptomatic stages when there is no evidence of anatomic changes on CT and MRI. Several radiolabeled PET tracers are already used to evaluate biological processes in vivo, (Camargo, 2001; Phelps, 2000; Silverman and Phelps, 2001; Van Heertum and Tikofsky, 2003) aiding in the differential diagnosis of AD from other conditions such as vascular dementia, frontotemporal dementia, DLB, and depression (Salmon et al., 1994; Van Heertum and Tikofsky, 2003). FDG PET is not only used in the differential diagnosis of AD, but also provides a diagnosis of prodromal AD two or more years before the full dementia picture is manifested. (Chang and Silverman, 2004; Silverman et al., 1999, 2001, 2002b) A pattern of reduced temporoparietal and posterior cingulate FDG uptake with sparing of the basal ganglia, thalamus, cerebellum, and primary sensorimotor cortex is the typical FDG 'AD signature' (Coleman, 2005; Devanand et al., 1997; Jagust et al., 2007; Salmon et al., 1994). Due to its high sensitivity (>90%) for detecting temporoparietal and posterior cingulate hypometabolism FDG–PET has improved diagnostic and prognostic accuracy in patients with probable AD (Kennedy et al., 1995; Salmon et al., 1994; Silverman et al., 2002a, 2001; Small et al., 1995). A similar pattern of hypometabolism has been reported in normal elderly ApoE ε4 carriers, (Reiman et al., 1996) MCI, (Chetelat et al., 2003; Chetelat et al., 2005; Mosconi et al., 2006a) asymptomatic subjects with mutations associated with familial AD, (Kennedy et al., 1995; Rossor et al., 1996) and in subjects with a strong family history of AD (Mosconi et al., 2006b). FDG hypometabolism is correlated with cognition (Furst et al., 2010; Landau et al., 2009) and is predictive of future cognitive decline (Drzezga et al., 2005, 2003; Mosconi et al., 2004).

PET has also been used to assess neuroreceptor/neurotransmitter systems in vivo. Nicotinic acetylcholine receptors (nAChRs) have been implicated in a variety of central processes, such as memory and cognition (Nordberg et al., 1991; Villemagne et al., 1998). Abnormally low densities of nAChRs have been measured in vitro in autopsy brain tissue of AD patients. PET studies revealed a reduced uptake and binding of ^{11}C-nicotine in the temporal and frontal cortices of AD patients (Nordberg, 1993a,b; Nordberg et al., 1991). Though the main focus of neuroceptor studies in AD has been the study of nAChRs, several other neurotransmitter/neuroreceptor systems, such as the dopaminergic, opiate and histaminergic systems amomg others, were also evaluated in dementing neurodegenative conditions. (Cohen et al., 1997; Higuchi et al., 2000; Kemppainen et al., 2000; Kepe et al., 2006; Piggott et al., 2003; Sedvall et al., 1987; Small, 2004; Versijpt et al., 2003; Walker et al., 2002). Enzymes involved in the degradation of neurotransmitters, such as brain acetylcholinesterase, have also been the focus of several studies (Kikuchi et al., 2013; Okamura et al., 2008).

2.2. Amyloid imaging

Aβ plaques and NFT are the hallmark brain lesions of AD. These microscopic aggregates are still well beyond the resolution of conventional neuroimaging techniques used for the clinical evaluation of patients with AD. Positron emission tomography (PET) is a sensitive molecular imaging technique that allows in vivo quantification of radiotracer concentrations in the picomolar range, allowing the non-invasive assessment of molecular processes at their sites of action, detecting disease processes at asymptomatic stages when there is no evidence of anatomic changes on computed tomography (CT) and magnetic resonance imaging (MRI) (Phelps, 2000). In the past most techniques focused on non-specific features derived mainly from dendritic and neuronal loss, which are relatively late and non-specific features in the progression of the AD, and secondary to the basic molecular dysfunction. While clinical criteria together with current structural neuroimaging techniques are sensitive and specific enough for the diagnosis of AD at the mid or late stages of the disease, the development of a reliable method of assessing Aβ burden in vivo has allowed early diagnosis at presymptomatic stages, more accurate differential diagnosis, as well as treatment follow up. (Villemagne et al., 2005). Moreover, Quantitative imaging of Aβ burden in vivo has provided insights into the relationship between Aβ burden and clinical and neuropsychological characteristics in the AD spectrum as well in other neurodegenerative conditions where Aβ plays a role. Furthermore, because new treatment strategies to prevent or slow disease progression through early-intervention are being evaluated, the accurate recognition of the underlying pathological process being targeted is essential. These fluid and imaging surrogate markers of pathology are being used for patient selection, target engagement and evaluation of efficacy of anti-Aβ therapy alongside clinical and neuropsychological tests.

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