IS AMYLOID PET IMAGING REALLY HELPFUL IN DIAGNOSING AND CHARACTERIZING DISEASE MODIFYING TREATMENT APPROACHES IN DEMENTIAS? NO

Marios Politis

Neurodegeneration Imaging Group (NIG); Safra Clinical Senior Lecturer & Consultant Neurologist, Department of Basic & Clinical Neuroscience; Institute of Psychiatry, Psychology & Neuroscience (IoPPN); King's College London, UK

Summary

Deposition of beta-amyloid in the brain is an early event in the pathological process of Alzheimer's disease and progresses with time; first appearing as diffuse plaques throughout the neocortex that then extend hierarchically into other brain regions. The mean distribution of amyloid deposits in amnestic mild cognitive impairment (aMCI) appears to be intermediate between the changes seen in the healthy and AD brain (Markesbery, 2010). However, many aged healthy people exhibit a similar degree of beta-amyloid brain deposition to that seen in aMCI patients, thus limiting the use of these lesions as a true pathologic marker to distinguish between normal aging and MCI (Price and Morris, 1999).

The Pittsburgh compound B (PIB), a radioactive analog of thioflavin T, labeled with [^{11}C] and used with PET over the past decade, has been able to image beta-amyloid plaques in neuronal tissue. [^{11}C]PIB PET has indicated that approximately two-thirds of aMCI patients and one-third of healthy elderly individuals show increased amyloid deposition (Pike et al., 2007; Rowe et al., 2007; Aizenstein et al., 2008). It has been shown that 82% of aMCI patients who were PIB-positive at baseline converted to AD after 3 years of follow-up as opposed to only 7% of PIB-negative patients (Okello et al., 2009). The prognostic value of a PIB-negative scan is less clear and annual conversion rates from aMCI to dementia in beta-amyloid-negative subjects have been reported to be in the range 0–18% (Okello et al., 2009; Wolk et al., 2009; Villemagne et al., 2011).

Although [^{11}C]PIB PET has been excellent for visualization of beta-amyloid *in vivo*, there are some notable shortcomings to its use. As with other beta-amyloid markers, [^{11}C]PIB PET uptake has poor specificity, has not demonstrated correlations with cognitive decline (Pike et al., 2007; Rowe et al., 2007; 2010) and remains relative stable once an early dementia phase is established despite the progressive decline in cognition (Engler et al., 2006; Jack et al., 2009; Scheinin et al., 2009). Most importantly, recent Phase 3 clinical trials of anti-beta-amyloid treatments, as exemplified by beta-amyloid immunotherapies with bapineuzumab (Salloway et al., 2014) and solanezumab (Doody et al., 2014), have failed to improve clinical outcomes, despite showing reduced cortical [^{11}C]PiB retention (Rinne et al., 2010).

The amyloid cascade hypothesis suggests that formation and accumulation of hyperphosphorylated tau in neurofibrillary tangles (NFTs) is triggered by toxic levels of beta-amyloid (Hardy and Selkoe, 2002). This view, however, has been challenged by several hypotheses including theories suggesting that tau inclusions appear before beta-amyloid plaques (Braak and Braak, 1991; Small and Duff, 2008; Jack et al., 2010; Braak and Del Tredici, 2011).

Neuropathological studies have shown that NFTs are increased in the amygdala, entorhinal cortex, subiculum and inferior parietal cortex in aMCI compared to controls, suggesting that NFTs are significantly increased at pre-dementia phases and maybe critical for the transition to AD (Braak and Braak, 1991; Guillozet et al., 2003). Further, altered tau levels in cerebrospinal fluid (CSF) have been detected before the emergence of cognitive symptoms of AD, suggesting that the formation of tau aggregates could be a potential pre-dementia marker (Buchhave et al., 2012). Another advantage of using tau as a diagnostic and treatment biomarker is that neuropathological studies indicate that tau aggregates develop with a specific distribution pattern in high-risk brain regions, with little between-patient variability (Braak and Braak, 1991).

Evidence from experimental studies indicates a direct link between tau and neurodegeneration, as hyperphosphorylated tau aggregates disrupt neuronal function ultimately leading to neuronal degeneration and death (Iqbal and Grundke-Iqbal, 2008; Alonso et al., 2008; Iqbal et al., 2009). Animal models of familial and sporadic tauopathies have shown that tau pathology alone can cause neurodegeneration (Götz et al., 2001; Lewis et al., 2001), and knockout of tau in APP transgenic mice seems to prevent memory deficits, beta-amyloid toxicity and premature death (Roberson et al., 2007; Ittner et al., 2010). Furthermore, tau aggregates and the progress of NFT pathology seem to be more closely

related to levels of cognitive decline and disease severity across the spectrum of aMCI and AD, whereas beta-amyloid depositions alone correlate poorly with the severity of dementia, suggesting that a continuum of tau-induced NFT pathology may underlie the transition between normal aging, aMCI and AD (Wilcock et al., 1982; Arriagada et al., 1992; Petersen et al., 2006; Bennett et al., 2004). However, it is possible that the beta-amyloid–tau interactions could be even more critical in AD related neurodegeneration (Musiek and Holtzman, 2012). For example, the presence of neuritic plaques, which contain both tau and beta-amyloid, is correlated more closely with dementia severity in AD than either plaques or tangles alone (Tiraboschi et al., 2004), supporting the concept that the interaction between beta-amyloid and tau is a driver of neurodegeneration in AD.

In conclusion there are currently no biomarkers sensitive to disease progression and cognitive decline that can be used at the time that matters the most: before the AD onset. Beta-amyloid PET imaging did not demonstrate correlations with cognitive decline and is weak in monitoring progression once early dementia is established. Beta-amyloid immunotherapies do not suppress dementia progression unless the drugs also diminish tau pathologies (Karran and Hardy, 2014). There is hope that tau PET with for example [^{11}C]PBB3 *(*Maruyama et al., 2013) or [^{18}F]T807 (Chien et al., 2013) would be able to be more biomarkers sensitive to disease progression and cognitive decline.

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