NeuroImage: Clinical 2 (2013) 356–365

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Review Article

Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease

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ARTICLE INFO

Article history:
Received 13 December 2012
Received in revised form 10 February 2013
Accepted 23 February 2013
Available online 5 March 2013

Keywords:
Amyloid PET imaging
Cognitively normal elderly
Preclinical Alzheimer's disease
Subjective cognitive decline
ApoE4
Longitudinal studies

ABSTRACT

Recent developments of PET amyloid ligands have made it possible to visualize the presence of Aβ deposition in the brain of living participants and to assess the consequences especially in individuals with no objective sign of cognitive deficits. The present review will focus on amyloid imaging in cognitively normal elderly, asymptomatic at-risk populations, and individuals with subjective cognitive decline. It will cover the prevalence of amyloid-positive cases amongst cognitively normal elderly, the influence of risk factors for AD, the relationships to cognition, atrophy and prognosis, longitudinal amyloid imaging and ethical aspects related to amyloid imaging in cognitively normal individuals. Almost ten years of research have led to a few consensual and relatively consistent findings: some cognitively normal elderly have Aβ deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, the prognosis for these individuals is worse than for those with no Aβ deposition, and significant increase in Aβ deposition over time is detectable in cognitively normal elderly. More inconsistent findings are still under debate; these include the relationship between Aβ deposition and cognition and brain volume, the sequence and cause-to-effect relations between the different AD biomarkers, and the individual outcome associated with an amyloid positive versus negative scan. Preclinical amyloid imaging also raises important ethical issues. While amyloid imaging is definitely useful to understand the role of Aβ in early stages, to define at-risk populations for research or for clinical trial, and to assess the effects of anti-amyloid treatments, we are not ready yet to translate research results into clinical practice and policy. More researches are needed to determine which information to disclose from an individual amyloid imaging scan, the way of disclosing such information and the impact on individuals and on society.

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2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.02.006

1. Introduction

This review will focus on amyloid imaging in cognitively normal elderly, asymptomatic at-risk populations, and individuals with subjective cognitive decline. It is one of two side-to-side review papers, the second one by Vandenberghe (2013–this issue) focusing on amyloid imaging in cognitively impaired populations. The present effort extends from a talk presented at the Alzheimer's Association International Conference (http://www.alz.org/aaic/overview.asp) in July 2012 on amyloid imaging in preclinical individuals. It will cover the prevalence of amyloid-positive cases amongst cognitively normal elderly, the influence of risk factors for AD, the relationships to cognition, atrophy and prognosis, longitudinal amyloid imaging and ethical aspects related to amyloid imaging in cognitively normal individuals. The goal was not to be exhaustive but to give weighted opinions on most challenging contemporary debates based on our current state of knowledge. Thus, some topics will not be covered, such as the relationships with other brain imaging modalities (e.g. fluoro-deoxyglucose (FDG)-PET, task-related and resting-state functional MRI, diffusion tensor imaging) and cerebrospinal fluid (CSF) biomarkers, or discussion on the similarities and differences between the various PET amyloid ligands.

β-amyloid (Aβ) deposition is one of the main hallmarks of Alzheimer's disease and is thought to play a central role in the neurodegenerative process characterizing this disease (Hardy and Selkoe, 2002; Masters et al., 2006). Neuropathological studies have shown more than 20 years ago that substantial level of Aβ deposition can be found in the autopsied brain of cases with documented normal cognition (Braak and Braak, 1997; Crystal et al., 1988; Katzman et al., 1988; Price and Morris, 1999). Recently, PET amyloid ligands have been developed, the first one (except from FDDNP see below) being the ^{11}C-Pittsburgh Compound B (^{11}C-PIB) PET ligand (Klunk et al., 2004), followed by the recently Food and Drug Administration (FDA)-approved ^{18}F-florbetapir (Choi et al., 2009; Wong et al., 2010) and other ^{18}F-labeled ligands (Herholz and Ebmeier, 2011). Thanks to these developments, we entered a new exciting area where it is possible to visualize plaques in the brain of living participants. This offers the unique opportunity to get further – including longitudinal – information in these individuals, so as to improve our understanding of the consequence of the presence of Aβ deposition in the brain of cognitively normal elderly, and more generally of the role of Aβ deposition in early AD pathological processes. Note that studies will be reviewed in what follows irrespective of the PET amyloid ligand being used, with the exception of studies using FDDNP (e.g. Small et al., 2006) that will not be included here as we aimed at specifically addressing issues related to Aβ while FDDNP binds to both Aβ and tau abnormalities.

2. The presence of Aβ in the brain of cognitively normal elderly and at-risk populations

2.1. The prevalence of amyloid-positive cases within cognitively normal elderly

Consistent with neuropathological studies (Price and Morris, 1999), neuroimaging amyloid-PET studies found amyloid-positive cases within cognitively normal ("healthy") older people. The first in-vivo ^{11}C-PIB PET study reported one ^{11}C-PIB-positive case amongst the control elderly (Klunk et al., 2004), and this has been consistently reported since then. A bimodal distribution of neocortical ^{11}C-PIB values is usually reported within elderly subjects with normal cognition (e.g. Klunk, 2011), though there is recent and accumulating evidence for intermediate cases (see below). A majority of healthy elderly shows low ^{11}C-PIB retention, but part of them shows distinctly

Table 1
Examples of the prevalence of amyloid-positive cases by clinical group. This illustrates the variability in the percentage of amyloid-positive cases amongst cognitively normal elderly (CNE) according to studies, probably due to variability in the methods and in the samples (see text for details). The prevalence in patients with mild cognitive elderly (MCI) and patients with Alzheimer's disease (AD) is also provided for the sake of comparison.

References	Amyloid ligand	CNE		MCI		AD	
		n	% Aβ +	n	% Aβ +	n	% Aβ +
(Rowe et al., 2010)	PIB	177	33%	57	68%	53	98%
(Jagust et al., 2010)	PIB	19	47%	65	72%	19	89%
(Mormino et al., 2012)[a]	PIB	75	15–35%	–	–	10	90%
(Okello et al., 2009)	PIB	26	0%	31	55%	-	-
(Lowe et al., 2009)	PIB	20	30%	23	40%	13	100%
(Jack et al., 2008)	PIB	20	30%	17	53%	8	100%
(Koivunen et al., 2011)	PIB	13	15%	29	72%	–	–
(Mintun et al., 2006)[a]	PIB	20	10–20%	–	–	10	90%
(Fleisher et al., 2011)[a]	Florbetapir	82	21–28%	60	40–47%	68	81–85%
(Rodrigue et al., 2012)	Florbetapir	87	20%	–	–	–	–
(Sperling et al., 2013)[a]	Florbetapir	78	14–23%	–	–	–	–
(Doraiswamy et al., 2012)	Florbetapir	69	14%	51	37%	31	68%
(Villemagne et al., 2011)	Florbetaben	32	16%	20	60%	30	97%
(Vandenberghe et al., 2010)	Flutemetamol	15	7%	20	50%	27	93%

[a] Studies that used different methods to define the threshold for amyloid-positivity, thus leading to different proportions of amyloid-positive cases; % Aβ +: percentage of amyloid-positive cases within the clinical group.