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Advances in perfusion magnetic resonance imaging in Alzheimer's disease

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Abstract

Recent research has demonstrated that brain circulation abnormalities, either during task-induced neural activity or at rest, are more commonly associated with Alzheimer's disease (AD) than was previously thought. This is consistent with the increasing attention to the early involvement of vascular risk factors in the development of AD, in addition to the dominating neurodegenerative pathology. Early detection of cerebral perfusion changes could help advance diagnosis and intervention therapies. The present article reviews advances in perfusion magnetic resonance imaging in the study of AD. In general, there are consistent accounts of cerebral hypoperfusion in the temporal and parietal lobes in people with clinically diagnosed AD. In the early stages of the disease, transient hyperperfusion may occur particularly in the prefrontal cortex, possibly as a compensatory effect. Nevertheless, significant variability in the details of perfusion patterns is present in the early phases, making the use of these methods in early diagnosis difficult. Noninvasive perfusion-weighted magnetic resonance imaging methods have advantages over nuclear medicine imaging, especially for safe usage in long-term follow-up studies. Optimization of perfusion-weighted imaging techniques is crucial for any future clinical application. Additional studies are needed with optimization likely to come with 3T and higher field strength magnets.

Keywords: Alzheimer's disease; Cerebral blood flow; Cerebral blood volume; Magnetic resonance imaging; Perfusion; Dynamic susceptibility contrast; Arterial spin labeling; Mild cognitive impairment

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by an insidious onset and progressive deterioration and is the most common cause of dementia in later life [1]. Although characteristic neuropathologic changes are described (e.g., accumulation of β-amyloid plaques and neurofibrillary tangles that begin in the entorhinal cortex and medial temporal lobe [MTL] and extend gradually to the entire neocortex) [2], the cause is still not clear [3–6]. In recent years, cumulative evidence has called attention to the role of acquired vascular factors in older adults so that many risk factors, such as ischemic stroke, atherosclerosis, hypertension, diabetes, and cardiac disease, have been shown to result in cerebrovascular dysfunction and trigger AD pathology [7–10].

Advances in neuroimaging technology have significantly benefited AD research and clinical practice [11–13]. Conventional imaging (e.g., structural computed tomography and magnetic resonance imaging [MRI] of the MTL) has been recommended to help discriminate probable and possible AD from normal aging and to differentiate AD from

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other dementias [11,12]. Functional neuroimaging techniques that reflect neural activity and metabolic changes have been developed to detect brain functional changes in preclinical stages [13]. Particularly important to the present review, imaging techniques that are sensitive to hemodynamic properties have revealed new insights into cerebrovascular abnormalities associated with AD. In the past, cerebral perfusion mainly has been imaged by single-photon emission computed tomography (SPECT) and positron emission tomography (PET), both of which require radioactive agents. Perfusion-weighted MRI (perfusion MRI or PWI) has emerged as a noninvasive alternative. The continued advances in perfusion imaging, especially perfusion MRI, call for a comprehensive review of recent progress. In this article, we review recent reports on perfusion imaging in AD. Our focus is on the correlation between evidence of brain damage and function. We address the following questions: (1) Are characteristic perfusion patterns present (both hypoperfusion in clinically diagnosed AD patients and hyperperfusion changes in the early stage)? (2) Does PWI offer advantages to PET/SPECT in the study of AD? (3) What are the limitations of PWI and how can they be mitigated in AD research and clinical settings?

2. Methods

2.1. Search strategies

We searched MEDLINE for studies published between January 1, 1977 and December 31, 2009. The keywords that we used consisted of combinations of Alzheimer's disease, mild cognitive impairment, perfusion, perfusion MRI, hypoperfusion, cerebral blood flow, dynamic susceptibility contrast, and arterial spin labeling. With "*perfusion", "cerebral blood flow" and "Alzheimer's disease*" 584 articles were retrieved. With "*perfusion", "cerebral blood flow" and "mild cognitive impairment*", 79 articles were retrieved. With "*dynamic susceptibility contrast" and "Alzheimer's disease*", 14 articles were retrieved. With "*arterial spin labeling" and "Alzheimer's disease*" 12 articles were retrieved. A smaller number of articles were found with "*dynamic susceptibility contrast*" and "*mild cognitive impairment*" [3], and with "*arterial spin labeling*" and "*mild cognitive impairment*" [4]. These search outcomes were verified with the Canadian Institute for Scientific and Technical Information databases and consistent results were revealed.

2.2. Inclusion and exclusion criteria

All the retrieved peer-reviewed journal articles studying brain perfusion of patients with AD and/or mild cognitive impairment (MCI) using common perfusion techniques including PET, SPECT, and PWI were examined. To be considered, a study was required to have at least one type of PWI, either with or without the use of other neuroimaging techniques. In addition, studies using just PET or SPECT that have provided novel information contributing to the advances of AD perfusion were also considered and the outcomes from those studies were used to compare with those of PWI. Studies that focused on computational methods without acquiring any imaging data, used animal models without having human participants, or applied techniques other than PWI, PET, or SPECT were excluded.

2.3. Perfusion imaging techniques

To help readers better understand the result, we will first introduce the basics of perfusion imaging methods used in the studies under review.

2.3.1. Single photon emission computed tomography and positron emission tomography

Imaging with PET and SPECT has been the mainstream of perfusion studies for over two decades, whereas other methods such as dynamic perfusion computed tomography [14] and transcranial Doppler [15] have also been used by a limited number of AD studies. PET and SPECT were first applied in clinical and preclinical applications in cardiology, oncology, and neurology research in the 1970s. In the neurological domain, they provide information about brain circulation characteristics with parameters such as cerebral blood flow (CBF) and cerebral blood volume (CBV). Both SPECT and PET techniques inevitably rely on radioactive tracers as contrast media [16].

SPECT has been recognized as a reliable technique to measure brain blood flow-based hemodynamics. It uses ^{133}Xenon, ^{99m}Tc-hexamethylpropylamine oxime, ^{99m}Tc-Bicisate (ethyl cysteine dimmer), or ^{123}I inosine–5'-monophosphate as a radiotracer. Although the spatial resolution with SPECT is relatively low (usually on the order of 1 cm), it has had a large number of applications [16–18].

PET has comparatively higher sensitivity and spatial resolution than SPECT, and can be used to obtain data from low perfusion areas. With PET, contrast agents used for the measurement of CBF or CBV are either injected ($H_2{}^{15}O$) directly or inhaled through the respiratory system ($^{15}O_2$ and $C^{15}O_2$) into the blood. Perfusion maps are acquired through modeling blood sample passing across brain regions of interest [16,19]. Although both PET and SPECT are important imaging methods for evaluating brain perfusion, noninvasive PWI technologies with great potential have emerged.

2.3.2. Perfusion-weighted MRI

Compared with nuclear medical imaging (e.g., PET, SPECT), PWI is less expensive and less invasive and can be used repeatedly in the same subjects [16,20]. On the basis of the nature of the contrast agent, PWI can be divided into two categories: (1) a dynamic perfusion imaging subcategory (including dynamic contrast enhancement imaging and dynamic susceptibility contrast [DSC]) that requires exogenous contrast tracers, and (2) arterial spin labeling (ASL), which does not require exogenous contrast tracers.