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Visual ratings of atrophy in MCI: prediction of conversion and relationship with CSF biomarkers

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Abstract

Medial temporal lobe atrophy (MTA) and cerebrospinal fluid (CSF) markers of Alzheimer's disease (AD) pathology may aid the early detection of AD in mild cognitive impairment (MCI). However, the relationship between structural and pathological markers is not well understood. Furthermore, while posterior atrophy (PA) is well recognized in AD, its value in predicting conversion from late-onset amnestic MCI to AD is unclear. In this study we used visual ratings of MTA and PA to assess their value in predicting conversion to AD in 394 MCI patients. The relationship of atrophy patterns with CSF Aβ1–42, tau, and p-tau(181) was further investigated in 114 controls, 192 MCI, and 99 AD patients. There was a strong association of MTA ratings with conversion to AD ($p < 0.001$), with a weaker association for PA ratings ($p = 0.047$). Specific associations between visual ratings and CSF biomarkers were found; MTA was associated with lower levels of Aβ1–42 in MCI, while PA was associated with elevated levels of tau in MCI and AD, which may reflect widespread neuronal loss including posterior regions. These findings suggest both that posterior atrophy may predict conversion to AD in late-onset MCI, and that there may be differential relationships between CSF biomarkers and regional atrophy patterns.

Keywords: Alzheimer's Disease Neuroimaging Initiative (ADNI); Visual rating scales; Posterior atrophy; Medial temporal lobe atrophy; Magnetic resonance imaging (MRI); cerebrospinal fluid (CSF); Biomarkers; Mild cognitive impairment (MCI); Alzheimer's disease (AD); Conversion

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia (Hebert et al., 2003). With aging populations, the number of patients with AD will rise dramatically, with it estimated to affect 81 million people worldwide by 2040 (Ferri et al., 2005). It is generally believed that patients with AD go through a "prodromal" phase before developing clinical AD. One prodromal stage which is increasingly well recognized is mild cognitive impairment (MCI) which is characterized by cognitive deficits (in particular memory) that are not severe enough to make a diagnosis of dementia (Morris et al., 2001; Petersen et al., 2001).

Histopathological studies have shown that the hallmarks of AD, namely amyloid plaques and neurofibrillary tangles, precede neuronal loss in presymptomatic AD patients (Price and Morris, 1999), and are also present in MCI subjects (Jicha et al., 2006; Markesbery et al., 2006; Price and Morris, 1999). Consistent with histopathological findings, cerebrospinal fluid (CSF) studies suggest that changes in Aβ1–42, tau, and phosphorylated tau (p-tau) levels precede clinical symptoms in AD (Fjell et al., 2008). More specifi-

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cally, reduced levels of Aβ1–42 and elevated levels of tau and p-tau have been shown to reflect the presence of AD pathology (Blennow and Hampel, 2003) and predict progression from MCI to AD (Hansson et al., 2006). While concentrations of CSF Aβ1–42 have been shown to correlate well with density of plaques at postmortem (Strozyk et al., 2003), levels of tau and p-tau are not only correlated with density of neurofibrillary tangles (Tapiola et al., 1997), but are also indicative of neuronal injury. The accumulation of tau in neurons has been suggested to disrupt neuronal activity followed by the release of tau cytoskeletal elements into the extracellular space, which then appears in the CSF (Arai et al., 1995; Blennow et al., 1995).

A growing number of research studies have aimed to find imaging biomarkers that predict which patients with MCI will convert to AD. Hippocampal and medial temporal lobe atrophy on magnetic resonance imaging (MRI) is a characteristic and early feature of AD (Frisoni et al., 2010; van der Flier et al., 2011). The pattern of progression of atrophy through the brain appears to mirror that described for the appearance of tau pathology from autopsy studies (Braak and Braak, 1991; Likeman et al., 2005; Whitwell et al., 2008a). Both atrophy in the medial temporal lobe, in particular hippocampal atrophy, and CSF markers have been shown to be predictive of conversion from MCI to AD (Hampel et al., 2010a, 2010b; Hansson et al., 2006; Jack et al., 1999; Killiany et al., 2002; Whitwell et al., 2008b). As a result both MRI and CSF biomarkers have been included in proposed diagnostic criteria for AD (Albert et al., 2011; Dubois et al., 2007).

While a number of studies have examined associations between atrophy patterns and CSF biomarkers, these were often restricted to medial temporal lobe regions. For example, Aβ1–42 levels have been shown to be related to hippocampal volumes (Fjell et al., 2008) and hippocampal atrophy rates (Chiang et al., 2011; de Leon et al., 2006; Schuff et al., 2009) in MCI. Some studies have also reported associations of tau and p-tau levels with hippocampal volumes in MCI (Fjell et al., 2008) and AD (Hampel et al., 2005), however, others have not found such a relationship (Schuff et al., 2009). A study by Tosun et al. (2010) that used a region-unbiased approach to investigate relationships between atrophy and CSF markers across the brain found that tau and p-tau levels were associated with smaller caudate volumes, while baseline concentrations of CSF Aβ1–42 were associated with smaller gray matter volumes in lingual, pericalcarine, and postcentral cortices in AD.

In addition to the importance of medial temporal lobe atrophy in MCI and AD, posterior regions are increasingly recognized to be affected in AD (Jones et al., 2006; Karas et al., 2007). Posterior atrophy has been shown to be particularly prominent in early-onset AD cases (Frisoni et al., 2007; Ishii et al., 2005; Shiino et al., 2008), and aid distinction of AD from other dementias such as frontotemporal lobar degeneration (FTLD) (Du et al., 2007; Lehmann et al., 2012; Likeman et al., 2005), suggesting that it might be a useful additional biomarker for early-onset AD. However, the role of posterior atrophy in late-onset MCI is not well understood.

Visual rating scales are increasingly used to assess atrophy for routine clinical use (Scheltens et al., 1992, 1997). In the current study, visual rating scales are used to assess atrophy in the medial temporal lobe and in posterior cortical regions. The medial temporal lobe atrophy (MTA) scale (Scheltens et al., 1992) has been shown to discriminate well between AD and healthy controls (Scheltens et al., 1992, 1995), and to predict conversion from MCI to AD (Korf et al., 2004). We have recently developed a visual rating scale for posterior atrophy (PA), which includes the posterior cingulate gyrus, precuneus, and parietal lobe (Koedam et al., 2011; Lehmann et al., 2012). This scale has been shown to improve the distinction between patients with pathologically confirmed AD from those with pathologically confirmed FTLD, and may also be valuable in distinguishing early-onset AD from younger controls (Koedam et al., 2011; Lehmann et al., 2012).

The aims of this study were (1) to assess the value of MTA and PA visual ratings in predicting time to conversion from MCI to clinical AD, and (2) to investigate relationships between atrophy patterns and CSF levels of Aβ1–42, tau, and p-tau in controls, MCI and AD.

2. Methods

2.1. Subjects

All subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, M.D., Veterans Affairs Medical Center and University of California—San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the USA and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for