Published in final edited form as:
Neurodegener Dis. 2014 ; 13(0): 163–165. doi:10.1159/000355063.

Imaging and CSF Biomarkers in the Search for Alzheimer's Disease Mechanisms

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Abstract

Background—The pathophysiological process of Alzheimer's disease (AD) begins many years before the emergence of clinical symptoms (*preclinical AD)*. A hypothetical biomarker progression in the pathogenesis of AD has been suggested beginning with the deposition of Aβ, followed by increases in neurofibrillary tangles (NFT), synaptic loss, hippocampal atrophy and lastly, cognitive impairment.

Objective—We explored the effect of several risk factors for AD on the pattern of AD biomarker expression in normal subjects.

Methods—AD-biomarker evidence was examined at baseline in 96 cognitively normal elderly with none or at least one of the following: ApoE4+ allele, a maternal History of AD (mFHx), Sleep-disordered breathing (SDB), and longitudinal evidence of decline to MCI or AD (Decliners) at follow-up.

Results—Decliners and ApoE4+ subjects presented with expected reduced CSF Aβ42, elevated P-tau and T-tau. Decliners, in addition had FDG-PET hypometabolism in the Medial Temporal Lobe (MTL). Individuals with mFHx demonstrated no Aβ42 effect, but had elevations in P-tau and T-tau. SDB was found to be associated with elevated Aβ42, P-tau and T-tau, as well as reduced MTL MRglc.

Conclusion—Our results indicate heterogeneous biomarker expression suggesting diversity of AD pathways in at-risk presymptomatic subjects.

Keywords

Alzheimer's disease; biomarkers; cerebrospinal fluid; neuroimaging; maternal family history; sleep disordered breathing; ApoE4; mechanisms

Introduction

Alzheimer's disease is the most common form of dementia, and is characterized by amyloid beta (Aβ) plaques, neurofibrillary tangles (NFT), neuronal loss and inflammation [1]. A definitive diagnosis of AD can be made only through autopsy after death, but several

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imaging and cerebrospinal fluid (CSF) biomarkers have proven to be useful in showing biomarker evidence for AD pathology *in vivo*. Several studies have suggested that clinically determined risk factors increase the life time risk for AD [2]. Moreover, recent studies show that the presence of amyloid and tau may identify AD pathology in advance of clinical symptoms in cognitively *normal* older adults (*preclinical AD*)[3–7]. This *preclinical stage*, in which tissue damage is presumably mild, provides an opportunity for potential novel interventions with disease-modifying therapies and risk factor prevention [8].

According to the "*Amyloid Cascade Hypothesis*" [9], neurodegeneration in AD is caused by the deposition of Aβ which is the primary influence driving AD pathogenesis, including the formation of NFTs. The deposition of Aβ in late onset AD is proposed to result from an imbalance between Aβ production and Aβ clearance, but the interaction between impaired Aβ clearance and known risk factors for AD, as well as the sequence of events that trigger and follow this deposition are unknown. Other authors have shown at postmortem that tau pathology actually precedes the deposition of Aβ, thus raising uncertainty as to the initial insult [1]. As such, the ordering of patterns of biomarker expression and progression in AD is still controversial, and necessitates further study.

Using biomarkers for AD, we examined at cross-section cognitively normal elderly expressing several "established", and "proposed" risk factors for AD such as the presence of ApoE4 allele (ApoE4+), a maternal History of AD (mFHx), Sleep-disordered breathing (SDB), and longitudinal evidence of decline to MCI or AD (Decliners) at follow-up. A reference group of stable at follow-up individuals, without evidence for any known risk factors other than age, was used as controls. Our interest was to test the hypothesis that there is diversity of biomarker expression among at-risk groups (no-RF).

Methods

Ninety-six cognitively normal elderly (mean age 63.9±8.5, age range 50–86, 66% female) were selected from active NIH supported longitudinal studies at the NYU Center for Brain Health (CBH) and examined using established AD-biomarkers from CSF and FDG-PET as described in previous publications [4;10]. Subjects were recruited from multiple community sources. For this study, subjects were divided into five different groups: ApoE4+(n=30; mean age 62.4±6.2, SDB (n=22, mean age 65.2±6.5) (based on an apnea/hypopnea index [AHI4%] greater than 5), mFHx (n=32; mean age 62.8±6.2) (based on clinician confirmed maternal history of AD after age 65), Decliners (n=8; mean age 71.3±5.2; time to decline 2.1±1.43 years), and a group of 28 subjects that had none of the above risk factors and were stable at follow up (no-RF; mean age 63.9±4.0). 23 subjects had more than one risk factor. Biomarker evidence of AD was compared between risk factor groups and stable no-RFs using T-test or ANCOVA (controlling for age and gender) where appropriate. Model assumptions of normality, equality of variances, and independence were checked for all analyses. Log transformations were used where necessary to achieve normal distributions. Statistical significance was defined as $p<.05$ using SPSS (version 20.0; Chicago, IL).

Results

Compared to no-RF, Decliners and ApoE4+ subjects presented with the expected reduced levels of CSF Aβ42 and elevated P-tau and T-tau. Additionally, Decliners had reduced MTL MRglc. Subjects with mFHx demonstrated no Aβ42 effect, but had elevations in P-tau and total tau. The SDB group had significantly higher Aβ42, P-tau and total tau as well as reduced MTL MRglc. (See table for details.)

Conclusions

The *preclinical stage* preceding diagnosis of AD has been shown to begin many years before the manifestation of clinical symptoms [4;11–13]. It has been suggested that biomarkers of AD do not turn pathological in an erratic or unsystematic fashion, but that their development is in a predictably sequential manner, with the deposition of Aβ as the initial biomarker in the pathogenesis of AD[14]. This view is in contrast with: a) the known neuropathological staging of the disease [1], b) studies showing preclinical AD [15] and MCI subjects [16] with evidence for neurodegeneration without amyloid deposition, and c) reports of amyloid-independent mechanisms that contribute to synaptic dysfunction and/or neurodegeneration [17]. Additionally, biomarker measurements cannot be equated to substrate pathology due to their differential sensitivity where some pathophysiological changes may lie beneath the detection threshold of in vivo measurements [18]. Our results partially agree with this theoretical model by showing that the early involvement of Aβ42 applies to the Decliners and ApoE4+ groups. However, these groups also had tau pathology. Moreover, we also observed a diversity of biomarker expression associated with other potential AD pathways. Individuals with either mFHx or SDB showed a tau effect but not an Aβ42 effect along with more downstream evidence for tissue damage. Interestingly, the SDB group showed an elevation of Aβ42 in association with elevated tau and tissue damage which could be related to sleep-dependent loss of CSF Aβ circadian patterns [19].

Growing evidence suggests an emerging heterogeneity of biomarker expression in AD. A recent study analyzed non-demented carriers of the AD genetic risk variant rs3818361 in CR1 and found them to have lower amyloid burden as measured by PiB PET than non-carriers, suggesting the CR1 risk allele may increase AD risk, at least initially, through a non Aβ-pathway[20]. Another study of cognitively normal subjects, reported abnormal biomarkers of neurodegeneration in 25% of their PiB PET negative scans at baseline. These subjects were designated as “suspected non-AD pathway” even though their rate of decline was not different from their *AD-type counterparts* [15]. Clearly additional follow-up and post mortem studies are required as well as better calibration of the biomarker surrogates.

The largely cross sectional nature of our data limits our interpretation as we do not know the proportions of subjects from our risk groups that will go on to develop AD. At present our findings should be interpreted as suggestive and not definitive for the patterns of biomarker expression that underlie diverse risk factors for AD. We anticipate our active longitudinal studies and others will contribute to differentiating biomarker patterns that increase the risk for AD.

Acknowledgments

This study was supported by NIH grants AG13616, AG032554, AG035137, AG12101, AG008051, AG036502, AG022374 and HL118624-01, and from the Alzheimer's Association Grants IIRG-09-132030 and NIRG-11-205479 grants, and the Clinical and Translational Science Institute grant UL1 TR000038.

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Table 1

Biomarker expression of AD risk groups.

	P-Tau[a]	T-Tau[a]	Aβ42[a]	FDG-MTL[b]
Decliners	8.2↑	10.9↑	4.3↓	−3.2↓
ApoE4+	9.2↑	9.4↑	7.7↓	ns
mFHx	13.4↑	7.2↑	ns	ns
SDB	6.2↑	9.0↑	4.5↑	−3.9↓

[a] F-values from ANCOVA of CSF biomarkers correcting for age and sex

[b] T-values for baseline values

↑ Significantly higher value than controls at p<.05

↓ Significantly lower value than controls at p<.05