Title
The Progression of Beta-Amyloid Deposition in Alzheimer’s Disease as Assessed by PET Imaging

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Author
Malatt, Camille

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Abstract

Alzheimer’s Disease has increasingly become a national health concern with the growth of the aging population. While there are currently no effective disease-modifying treatments, there is a need for biomarkers that could be used in early diagnosis of the disease and in measuring efficacy of therapeutics in clinical trials. Beta-amyloid peptide in particular is thought to play a critical role in the pathogenesis of the disease. Especially with the advent of Florbetapir, a new compound that will facilitate more accessible and accurate amyloid-PET imaging, beta-amyloid could become an even more valuable biomarker. While useful in early detection of AD, it is not clear if it has utility in staging AD’s progression. The biomarker cascade model states that beta-amyloid levels plateau before the onset of clinical symptoms, and thus do not have a direct relationship with cognitive decline, suggesting that amyloid-PET imaging provides little information about disease stage. However, most data supporting this hypothesis have been based on quantification of amyloid load using standardized uptake value ratios (SUVr), which is limited in neurodegenerative disease where progressive regional atrophy can be confounded with levels of regional amyloid deposition. For example, SUVr relies on warping all patients’ brain images to a standardized “template” space, yet success in matching a brain to template space is inversely related to the degree of brain atrophy. Also, SUVr is typically measured across a subset of select cortical regions that are known to show elevated amyloid in early disease. We challenge this model by studying the change in both global and regional deposition of beta-amyloid in healthy controls, mild cognitive impairment (MCI) patients, and AD patients using quantification of amyloid binding in each subject’s “native-space,” along with atrophy correction. We hope to show that beta-amyloid levels do not completely saturate, but instead continue to increase during the progression of the disease. This would suggest that amyloid-PET imaging contains some information about the stage or severity of disease in both MCI and AD patients, and thus would have some value in aiding in predictive prognosis.

Background

Alzheimer’s Disease is the number one cause of dementia and the 6th leading cause of death in the United States. Approximately 5 million Americans are currently living with the disease, and this number is expected to triple by the year 2050. AD places an emotional burden on families, as well as a huge financial burden on society. The cost of health care, long-term care, and hospice for people with AD and other dementias was an estimated $200 billion in 2012, and this number will only continue to rise. This is an urgent issue, and there is much work being done to understand the neural mechanisms of the disease and to seek potential preventive interventions and treatments.
There is currently a search for in vivo biomarkers that can be measured for diagnostic purposes in AD, as well as for use in the development of therapeutics. Beta-amyloid is a peptide that has been implicated as a potential important biomarker. There is a general consensus that cleavage from its precursor protein is critical to the pathophysiology. Accumulation of the cleaved peptide into plaques disrupts processes involved in memory formation and damages neighboring neural tissue. Other potential biomarkers include formation of neurofibrillary tangles (NFT) by tau protein and cerebral atrophy. Affected areas early in the disease include the medial temporal cortex, especially the entorhinal and perirhinal cortices, which play a role in episodic memory formation. This damage is responsible for the symptoms of memory impairment that appear even in the earliest stages of AD, as well as in MCI patients, some of whom eventually progress to AD. The disease then spreads to the limbic and paralimbic regions of the temporal lobe, involving the transentorhinal and inferior temporal neocortical regions, the hippocampus, the subicular complex, and the basal forebrain, as well as neocortical association areas in the frontal, parietal, and occipital lobes. It is likely that this involvement explains the further impairment of higher cortical functions in patients as the disease progresses.

In 2011, the FDA approved the Florbetapir F18 injection (Amyvid) as a radiopharmaceutical compound to be used in amyloid-PET imaging to diagnose AD. This compound binds to amyloid aggregates in the brain, allowing the density of these plaques to be estimated. Previously, PiB PET was the most widely adopted amyloid PET tracer, but has been limited to research because of its short half-life. Florbetapir has a longer half-life, so that it can be prepared remotely and delivered more widely. Furthermore, it exhibits very high affinity-specific binding to beta-amyloid, binding to vulnerable brain regions in AD patients, while binding minimally in normal subjects. The test has 92% sensitivity and 95% specificity, and has been shown to have a wide effective dose range and high test-retest reliability for both quantitative assessment with an algorithm and visual assessment by people trained for analysis. This imaging may aid in ruling out AD, identifying MCI patients at risk for progression to AD, and predicting responses to medication.

While it has been shown that beta-amyloid protein is a potential biomarker for the diagnosis of AD, a more controversial issue is whether or not it can be used in grading the progression of the disease. There are some models that propose that levels of beta-amyloid protein become abnormal first while the patient is still cognitively normal, reach a plateau, and remain relatively static thereafter. This is followed by the appearance of NFTs and cerebral atrophy, and finally the onset of cognitive symptoms. This suggests that dementia is the manifestation of the end stage of many years of accumulation of pathological changes, and that clinical symptoms are directly related to biomarkers of neurodegeneration rather than biomarkers of beta-amyloid deposition.
Figure 1. Biomarker cascade hypothesis proposed by Jack et. al, 2013

Figure 1 illustrates the proposed model for biomarker staging and disease progression. Part A shows the basic model, and Part B emphasizes how the biomarkers differ from each other prior to symptom onset. The model’s implication for clinical trials is that beta-amyloid levels should not be used as evidence of therapeutic modification of the AD pathological process, as it has little relation to change in cognition. However, it suggests that targeting beta-amyloid before the onset of symptoms, may provide better clinical outcomes. This calls for the detection of beta-amyloid deposition very early on predicting future progression to AD.
**Project Goals**

With the growing acceptance of the biomarker cascade hypothesis, we wanted to test this model, specifically with regards to changes in the levels of beta-amyloid peptide. Our goal was to study this further by the comparison of global and regional beta-amyloid deposition in healthy controls, MCI patients, and AD patients. We hypothesized that using our program, PET QUANT, to analyze the PET scans, amyloid may not completely saturate before the onset of cognitive symptoms. PET QUANT accounts for an individual’s anatomy and possible atrophy, and should give more accurate quantification of amyloid binding. In addition, since there is a progression of amyloid spread, it seems that we would be able to gain more information by looking at the whole cortex rather than just a few select regions that are usually studied because they deposit early on in the disease (isthmus cingulate, posterior cingulate, and precuneus).

This would have significant implications for the use of amyloid-PET imaging in AD in the future. Higher than normal levels of beta-amyloid deposition both globally and in specific regions of the brain in MCI patients would indicate future progression to AD, and could even provide an estimated timeline for when this might happen. This would be particularly useful with the creation of effective therapeutics, in which earlier intervention would result in the best clinical outcome. Normal levels would help to rule out AD, allowing for investigation into other possible causes of cognitive impairment, some of which could be easily treatable. Imaging could also be utilized in clinical trials to evaluate the efficacy of the treatment. Improvement of symptoms is less precisely evaluated, and would lag behind changes in beta-amyloid levels. Quantitative analysis with imaging would be more accurate, and would make for faster clinical trials.

**Methods**

Our study included 464 subjects: 139 normal controls, 266 MCI patients, and 59 AD patients, all taken from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. Subjects were all between the ages of 60 and 90, and were placed into the various groups based on clinical measures such as Mini-Mental State Examination (MMSE) scores. Recruited AD patients were relatively early in the course of the disease, with MMSE scores ranging from 20 to 26 out of a possible score of 30.

Each subject’s brain was imaged using MRI and Florbetapir PET by ADNI. These images were uploaded into our PET QUANT software, which quantified levels of beta-amyloid peptide in all regions of the brain. The software compares uptake to that of the cerebellum, which has been shown to have consistently low uptake in MCI and AD patients. This value is given as a cortico/cerebellar native-space standard uptake ratio (nSUVr). Output was then used to calculate a whole cortex average amyloid burden and a regional amyloid burden based on the average of the isthmus cingulate, posterior cingulate, and precuneus regions.

Individual scans determined to be amyloid-positive were selected for further analyses. As the output values of amyloid burden calculated by the software were slightly lower than those in published studies, cut-off values were determined using ROC curve analysis with data from these same subjects as analyzed by Berkeley researchers.
subjects were found to be positive for amyloid based on global values. Global and regional amyloid burden were then averaged within each of the three groups (normal controls, MCI, and AD) and these means were compared with t-tests to see if the differences between them were statistically significant. Further, we examined the correlation of global and regional amyloid burden with cognitive test scores (clinical dementia rating scale (CDR), Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) 13, and MMSE scores) using linear regression analysis. All statistical analyses were done using SPSS, and controlled for age, sex, and education.

Additional analyses were done with both amyloid-positive and -negative subjects. With additional volumetric output from the software using MRI, all MCI patients were determined to be positive or negative for hippocampal atrophy. The volumetric data was used to calculate a hippocampal occupancy score to provide an estimate of medial temporal lobe atrophy, computed as a ratio of hippocampal volume to the sum of the hippocampal and inferior lateral ventricle volumes. Right and left values were averaged. The cut-off was a threshold of -1.02 SDs below the mean value of the normal controls, controlled for age, sex, and education. The percentage of conversion of MCI subjects to AD was compared across 4 classifications of individuals: amyloid-positive/atrophy-positive, amyloid-positive/atrophy-negative, amyloid-negative/atrophy-positive, and amyloid-negative/atrophy-negative.

Results

![Figure 2. Whole cortex amyloid binding across clinical diagnoses](image-url)
Figure 3. Regional amyloid binding across clinical diagnoses

Figures 2 and 3 show differences in amyloid binding between groups. Figure 2 shows amyloid levels averaged across the whole cortex, then averaged within diagnostic category. Figure 3 shows amyloid levels averaged across the 3 selected regions (isthmus cingulate, posterior cingulate, and precuneus). The difference between the normal and MCI groups, as well as the difference between the MCI and AD groups, are statistically significant for both graphs (p<0.01). In addition, the Cohen’s d values were calculated, which show the magnitude of the differences. When looking at the whole cortex, there is a large magnitude of difference (d=0.756) between the MCI and AD groups, while there is a medium magnitude of difference (d=0.496) when looking at regional amyloid.
Figure 4. Relationship between whole cortex amyloid binding and ADAS-Cog 13 score

Figure 5. Relationship between regional amyloid binding and ADAS Cog-13 score
Figures 4 and 5 show the relationship between amyloid binding and ADAS-Cog 13 score when measuring amyloid binding across the whole cortex and only across the selected regions. A higher ADAS score indicates increased cognitive impairment. The correlations are 0.393 and 0.328, both of which are statistically significant (p<0.01). These would be considered moderate correlations.

Figure 6. Relationship between whole cortex binding and CDR Global score
Figures 6 and 7 show the relationship between amyloid binding and CDR Global score when measuring amyloid binding across the whole cortex and only across the selected regions. A higher CDR Global score indicates increased cognitive impairment. The correlations are 0.356 and 0.292, both of which are statistically significant (p<0.01). These would be considered moderate and mild correlations, respectively.
Figure 8. Relationship between whole cortex amyloid binding and MMSE score

Figure 9. Relationship between regional amyloid binding and MMSE score
Figures 8 and 9 show the relationship between amyloid binding and MMSE score when measuring amyloid binding across the whole cortex and only across the selected regions. A lower MMSE score indicates increased cognitive impairment. The correlations are -0.286 and -0.243, both of which are statistically significant (p<0.01). These would be considered mild correlations.

![Conversion of MCI subjects to AD based on atrophy and amyloid status](image)

**Figure 10. Conversion of MCI subjects to AD based on atrophy and amyloid status**

This survival curve shows the percentage of conversion of the 266 original MCI subjects to AD over a period of 108 months based on the above classifications. Of the 57 atrophy-positive/amyloid-positive subjects, 50.9% converted to AD. Of the 86 atrophy-negative/amyloid-negative subjects, 1.2% converted to AD. Of the 46 atrophy-positive/amyloid-negative subjects, 8.7% converted to AD. Of the 80 atrophy-negative/amyloid-positive subjects, 23.7% converted to AD.

**Discussion**

We hypothesized that our results would show beta-amyloid does not completely saturate before the onset of cognitive symptoms. There was a statistically significant difference between the amyloid burden of MCI and AD subjects, as well as that of normal and MCI subjects. Based on the Cohen’s d values, there was a large magnitude of difference between the MCI and AD groups when measuring global amyloid, while there was a medium magnitude of difference when measuring regional amyloid. This suggests continued increase in amyloid burden rather than complete saturation between the MCI and AD stages, at a point when cognitive decline has already occurred. In addition, a greater difference is measured when looking at global amyloid levels than regional amyloid levels, suggesting that global measurements provide additional information.
Furthermore, positive correlations were present between performance on cognitive tests and amyloid burden. The correlations ranged from mild to moderate, and were all statistically significant. ADAS-Cog 13 scores showed the largest correlation, and all cognitive tests showed greater correlation with global amyloid burden than regional amyloid burden. This suggests that amyloid burden is indeed related to a person’s cognitive state.

Despite the statistical significance of these results, the clinical significance remains unclear. Although there were differences between the mean amyloid burden of each group, they were relatively small. Furthermore, the spread around the mean of each group was large. Thus, for any specific individual, it would be difficult to predict the stage of disease and prognosis using his or her measured amyloid level. Similarly, although cognitive state overall correlated with level of amyloid burden, there were many subjects that had very different scores but similar amyloid level. Therefore, when measuring amyloid on an individual basis rather than on a population level, the information may not be as useful.

As these results did not clearly support the predictive value of amyloid, further analyses were done looking at the predictive value of both amyloid and atrophy simultaneously. Measuring the percentage of MCI subjects who converted to AD based on their amyloid burden and level of atrophy seemed to provide useful information. About half of the subjects that were positive for both amyloid and atrophy converted from MCI to AD, and only about 1% of the subjects that were negative for both converted. Interestingly, about 9% of subjects that were amyloid-negative and atrophy-positive converted, and about a quarter of subjects that were amyloid-positive and atrophy-negative converted. The latter group may be interpreted as being at an earlier stage of AD in which amyloid had deposited but had not resulted in atrophy yet, and thus having a moderate percentage of conversion. The former group may be interpreted as having atrophy for an alternate reason (such as other dementias, aging, etc.) and thus had a much lower percentage of conversion. These results suggest that measuring amyloid burden and atrophy together may provide a much improved method for predicting disease progression in these patients.

A limitation of this study is that it does not look at longitudinal data, which would allow us to see amyloid changes within individuals. This analysis could be more enlightening given the variation between individual subjects. Also, some individuals have higher amyloid burden but are clinically and cognitively at the “mild” stage of disease, while others have lower amyloid burden but have more severe dementia. What is it that distinguishes these populations? Some things to consider are cognitive reserve, which may allow some subjects to withstand higher amounts of amyloid, co-morbidities, and levels of atrophy. These future directions may provide additional insight.

**Conclusion**

We sought to challenge the biomarker cascade hypothesis, and while our results do suggest that amyloid does not completely saturate before changes in cognition, these
changes in amyloid burden are small and are seen in the population as a whole. Thus, prognosis and disease progression would be difficult to predict on an individual level without the combination of other biomarkers. Furthermore, our data do show a correlation between amyloid burden and cognitive status, but one that is weak, and again may not be helpful clinically. Additional information can likely be gained from measuring a patient’s atrophy as well as their amyloid level, and this can be useful in predicting a patient’s trajectory from MCI to AD.

References


