Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study

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Summary

Background Models of Alzheimer's disease propose a sequence of amyloid β (Aβ) accumulation, hypometabolism, and structural decline that precedes the onset of clinical dementia. These pathological features evolve both temporally and spatially in the brain. In this study, we aimed to characterise where in the brain and when in the course of the disease neuroimaging biomarkers become abnormal.

Methods Between Jan 1, 2009, and Dec 31, 2015, we analysed data from mutation non-carriers, asymptomatic carriers, and symptomatic carriers from families carrying gene mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) enrolled in the Dominantly Inherited Alzheimer's Network. We analysed ^{11}C-Pittsburgh Compound B (^{11}C-PiB) PET, ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET, and structural MRI data using regions of interest to assess change throughout the brain. We estimated rates of biomarker change as a function of estimated years to symptom onset at baseline using linear mixed-effects models and determined the earliest point at which biomarker trajectories differed between mutation carriers and non-carriers. This study is registered at ClinicalTrials.gov (number NCT00869817)

Findings ^{11}C-PiB PET was available for 346 individuals (162 with longitudinal imaging), ^{18}F-FDG PET was available for 352 individuals (175 with longitudinal imaging), and MRI data were available for 377 individuals (201 with longitudinal imaging). We found a sequence to pathological changes, with rates of Aβ deposition in mutation carriers being significantly different from those in non-carriers first (across regions that showed a significant difference, at a mean of 18·9 years [SD 3·3] before expected onset), followed by hypometabolism (14·1 years [5·1] before expected onset), and lastly structural decline (4·7 years [4·2] before expected onset). This biomarker ordering was preserved in most, but not all, regions. The temporal emergence within a biomarker varied across the brain, with the precuneus being the first cortical region for each method to show divergence between groups (22·2 years before expected onset for Aβ accumulation, 18·8 years before expected onset for hypometabolism, and 13·0 years before expected onset for cortical thinning).

Interpretation Mutation carriers had elevations in Aβ deposition, reduced glucose metabolism, and cortical thinning compared with non-carriers which preceded the expected onset of dementia. Accrual of these pathologies varied throughout the brain, suggesting differential regional and temporal vulnerabilities to Aβ, metabolic decline, and structural atrophy, which should be taken into account when using biomarkers in a clinical setting as well as designing and evaluating clinical trials.

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Introduction

Alzheimer's disease presents as a progressive loss of cognitive function, leading to severe impairment and loss of independence. Alzheimer's disease's long preclinical phase has bolstered efforts to identify in-vivo biomarkers to aid disease diagnosis and prognosis.[1] Models of Alzheimer's disease pathophysiology theorise a temporal sequence in which disruptions in amyloid β (Aβ) production, clearance, or both initiates a biological cascade that leads to Aβ plaque formation that spreads throughout the cortex, followed by tauopathy, neuronal dysfunction, neuronal death, and ultimately dementia.[2,3]

PET and MRI can be used to assess both the amount and location of Aβ plaques, tauopathy (eg, tau-containing neurofibrillary tangles and neuropil), altered glucose metabolism, and structural decline. The temporal sequence of these biomarkers provides information about the pathogenesis of Alzheimer's disease. Determining the order of changes in sporadic

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Research in context

Evidence before this study

We reviewed previous work on longitudinal neuroimaging markers of Alzheimer's disease pathology with a focus on autosomal dominant Alzheimer's disease. We searched PubMed and Google Scholar for all articles published from database inception to Oct 31, 2017, with no language restrictions, for the keywords "Alzheimer's", "Alzheimer", "longitudinal", "positron emission tomography", "PET", "MRI", "atrophy", "FDG", "hypometabolism", "familial", and "autosomal". Theories proposed initially in 2010 by Jack and colleagues and revised in 2013 posited temporal trajectories of Alzheimer's disease biomarkers relative to each other and clinical decline. Work by Bateman and colleagues in 2012, Benzinger and colleagues in 2013, and Fleisher and colleagues in 2015 depict such temporal ordering of biomarkers in autosomal dominant Alzheimer's disease populations derived from cross-sectional analyses. There was also a small subset of longitudinal studies, but these had one or more limitations such as small populations (n<50), examination of only one biomarker, not accounting for regional differences or correlations in the brain, or a short duration of longitudinal follow up.

Added value of this study

To our knowledge, our study presents the first known work examining both the longitudinal temporal trajectories and the spatial patterns of Alzheimer's disease pathology in autosomal dominant Alzheimer's disease cohorts using neuroimaging. This work also presents the largest known cohort to date of individuals with autosomal dominant Alzheimer's disease studied longitudinally with multiple neuroimaging biomarkers. Longitudinal analyses can provide a more accurate and powerful way to model the temporal emergence of pathology in autosomal dominant Alzheimer's disease. We find that mutation carriers first display amyloid β accumulation, followed by hypometabolism, and finally structural atrophy; this is consistent with theoretical models and cross-sectional estimates from autosomal dominant Alzheimer's disease. Most importantly we consider such temporal relationships not in one singular summary measure, but characterise these trajectories throughout the brain. We found that the accrual of pathology varied throughout the brain and by method in terms of the time of initial emergence and the rates of longitudinal change. These findings suggest region-specific vulnerabilities to β-amyloidosis, metabolic decline, and atrophy that change over the course of the disease.

Implications of all the available evidence

Our results build upon existing evidence characterising biomarkers in clinical and preclinical Alzheimer's disease. Our findings suggest that imaging biomarkers follow a sequential pattern, with β-amyloidosis, hypometabolism, and structural atrophy emerging more than 20, 15, and 10 years, respectively, before the expected onset of dementia. Although there is a general hierarchical pattern, there was considerable regional heterogeneity. The most common deviation from the pattern of β-amyloidosis, followed by hypometabolism, followed by structural atrophy was that regions showed an increase in β-amyloidosis and structural atrophy but no evidence of metabolic decline. Furthermore, rather than being homogeneous, the same biomarker often shows different longitudinal trajectories across brain regions. Characterising the temporal and regional dynamics of biomarkers in Alzheimer's disease provides insight into disease pathophysiology. This information is crucial to decide how to best use neuroimaging biomarkers in clinical trials for participant selection as well as for outcomes measures.

Alzheimer's disease is problematic because it is difficult to predict an individual's relative position in the disease. Autosomal dominant Alzheimer's disease is well suited to study biomarker trajectories owing to the virtually complete penetrance of the mutations and consistency of symptom onset within families.[4,5] The conserved onset age within families and mutation types allows individuals to be staged relative to their expected onset of symptoms.

Research on autosomal dominant Alzheimer's disease has revealed a temporal ordering of biomarkers consistent with theoretical models,[6–8] and indicates that pathology progressively appears in new regions of the brain as the disease worsens.[7] These findings have primarily relied on cross-sectional analyses, with few longitudinal studies done, and mainly using small cohorts.[7,9–16] Longitudinal analyses can provide a better estimate of the true pathological trajectories.[17,18] This is crucial because interventional trials such as the Dominantly Inherited Alzheimer Network (DIAN) Trials Unit,[19] the Alzheimer's Prevention Initiative (API),[20] and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study (A4)[21] will all evaluate alterations in longitudinal biomarker trajectories.

The DIAN observational study[4] has established a large cohort of families with autosomal dominant Alzheimer's disease and longitudinal Aβ, metabolic, and structural neuroimaging assessments of family members. Our current work compares rates of biomarker change in a large population of mutation carriers and non-carriers throughout the entire brain. In this way we can visualise when pathology biomarkers first emerge and how they spread throughout the course of the disease.

Methods

Study design and participants

Individuals from families known to have mutations in the presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) genes were recruited from 14 sites participating in the DIAN observational study in the USA, UK, Germany, and Australia. All participants with genetic, clinical, and neuroimaging