Featured Article

Incidence of cognitively defined late-onset Alzheimer's dementia subgroups from a prospective cohort study

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Abstract

Introduction: There may be biologically relevant heterogeneity within typical late-onset Alzheimer's dementia.

Methods: We analyzed cognitive data from people with incident late-onset Alzheimer's dementia from a prospective cohort study. We determined individual averages across memory, visuospatial functioning, language, and executive functioning. We identified domains with substantial impairments relative to that average. We compared demographic, neuropathology, and genetic findings across groups defined by relative impairments.

Results: During 32,286 person-years of follow-up, 869 people developed Alzheimer's dementia. There were 393 (48%) with no domain with substantial relative impairments. Some participants had isolated relative impairments in memory (148, 18%), visuospatial functioning (117, 14%), language (71, 9%), and executive functioning (66, 8%). The group with isolated relative memory impairments had higher proportions with *APOE ε4*, more extensive Alzheimer's-related neuropathology, and higher proportions with other Alzheimer's dementia genetic risk variants.

Discussion: A cognitive subgrouping strategy may identify biologically distinct subsets of people with Alzheimer's dementia.

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Keywords: Alzheimer's disease; Cognition; Subgroups; Endophenotypes; Heterogeneity; Genetics; Neuropathology

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1. Introduction

There may be considerable heterogeneity in clinical presentation among people with incident Alzheimer's dementia begging the question of whether Alzheimer's dementia in older adults should be considered a single entity or meaningfully subdivided into distinct disorders. Meaningfully subdividing a condition into distinct groups is essential to the strategy of personalized medicine [1–3]. Data are currently lacking, demonstrating a scalable approach for meaningfully subdividing Alzheimer's dementia.

Recent proposed guidelines identified atypical Alzheimer's disease subtypes usually having younger age of onset, including logopenic primary progressive aphasia, dysexecutive Alzheimer's disease, and posterior cortical atrophy [4]. Intriguingly, each of these subtypes is associated with prominent impairment in a single nonmemory domain—language, executive functioning, and visuospatial functioning, respectively—with relatively intact memory performance. These previously identified atypical Alzheimer's disease subtypes may represent extremes of a spectrum of disease phenotypy.

We followed insights from neuropsychology, where practitioners have considered patterns of relative impairments across cognitive domains to facilitate diagnosis since the earliest days of the field [5]. We used cognitive data to determine the distribution at Alzheimer's dementia diagnosis for memory, language, executive functioning, and visuospatial abilities in a community-based prospective cohort study. We determined individual averages across domains and identified domains with substantial impairments relative to that average. We defined subgroup membership based on which domains had relative impairments. We compared demographic, neuropathology, and genetic findings across subgroups to test the hypothesis that we could use cognitive data to identify biologically distinct late-onset Alzheimer's dementia subgroups.

2. Methods

We followed the STROBE guidelines (Appendix A) [6]. All steps are summarized in Appendix B.

2.1. Study population

The source population for the Adult Changes in Thought (ACT) study consists of community-living members of Group Health, a health maintenance organization in the western Washington state. A random sample of community-living Group Health members aged ≥65 years without established dementia diagnoses was invited to an enrollment visit in 1994 to 1996. The Cognitive Abilities Screening Instrument (CASI) was administered. The CASI is a 100-point scale that assesses several cognitive domains. Individuals with scores >85 were invited to enroll. Those with scores of ≤85 were further evaluated with a neuropsychological battery and comprehensive neurological evaluation. The neuropsychological battery included clock drawing [7], verbal fluency [8], Mattis Dementia Rating Scale [9], Boston naming [8], verbal-paired associations and recall, logical memory and recall [10], Word List Memory [8], Constructional Praxis and recall [8], Trails A and B [11], and Information and Comprehension subtest items [10].

All cognitive and clinical data were reviewed in a multidisciplinary consensus conference to determine dementia status; data from each case are discussed and forms with standardized criteria are filled out. Composite scores were not available at the time of consensus conferences and were not considered. Individuals free of dementia were invited to enroll in the longitudinal study. Identical methods were used for an expansion cohort in 2000 to 2003. In 2005, the study began continuous enrollment in which identical methods are used to enroll new participants each month. This report considers all enrollees through April 2015, the most recent data freeze.

Once enrolled, participants are administered using the CASI every 2 years. The same procedures are used to identify incident dementia [12] and probable or possible Alzheimer's disease using NINCDS-ADRDA criteria [13], referred to here as Alzheimer's dementia.

Other than being a Group Health member, being free of dementia, and volunteering for a longitudinal study, there are no additional inclusion or exclusion criteria for ACT. ACT study evaluates participants in their own homes or at a study clinic for study visits [14].

We focus here on individuals who developed incident Alzheimer's dementia. The derivation of the analytic cohort is provided in Fig. 1. The study was reviewed by Group Health and University of Washington Institutional Review Boards. Participants gave written informed consent.

2.2. Ascertainment of subgroups

An expert panel (E.T., A.J.S., and J.M.) considered each cognitive item and assigned each item to a single cognitive domain—memory, visuospatial functioning, language, executive functioning, or other. We used modern psychometric methods to obtain scores for each domain. Composite scores have been recommended to address idiosyncrasies of individual cognitive tests. Modern psychometric approaches have proven to have incrementally better validity data than scores derived from standard approaches [15–17], and they are specifically recommended for genetic analyses [18]. We recoded observed item responses to avoid sparse response categories and limit to ≤10 response categories (see Appendix C–F). We used Mplus 7.4 [19] to fit confirmatory factor analysis single factor or bifactor models for each domain separately. All scores were scaled to have mean 0 and standard deviation (SD) 1 in all those with incident AD who had all four scores ($n = 825$). Psychometric modeling details for each domain are provided in Appendix C–F.

We determined each person's average across the four cognitive domain scores. We determined relative