alzheimer's research&therapy

COMMENTARY

Defining and describing the pre-dementia stages of familial Alzheimer's disease

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Abstract

With the prospect of prevention trials for familial Alzheimer's disease on the horizon, understanding the natural history of the illness has never been so important. Earlier this year in *The Lancet Neurology*, Acosta-Baena and colleagues published the results of the largest and longest retrospective study of pre-dementia clinical stages in familial Alzheimer's disease to date. By reviewing serial neuropsychological assessments of individuals from a large Colombian kindred affected by the E280A mutation in the Presenilin 1 gene, they defined three stages of pre-dementia cognitive impairment. Using survival analyses, the authors estimated the median age at onset and rate of progression through each of these stages towards dementia and ultimately death. Their study provides valuable insights into the time course of cognitive decline associated with this mutation. Furthermore, the study highlights some of the challenges of defining pre-dementia clinical stages in familial Alzheimer's disease and the need for the field to develop a consistent terminology.

It is now well established that symptoms of Alzheimer's disease (AD) dementia are preceded by a long period of gradual accumulation of pathological changes [1]. The growing view that disease-modifying therapies may only be effective if used relatively early in this process has shifted attention towards the pre-dementia phases of the disease. This shift in focus has been accompanied by increasing recognition of the importance of familial AD. The study of individuals carrying rare, autosomal dominantly inherited mutations in the amyloid precursor protein (*APP*), Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) genes provides unique opportunities to observe the earliest manifestations of the pathological process. With the design of prevention trials for these individuals already underway [2,3], there is an urgent need to better understand and define the pre-dementia stages of familial AD.

Acosta-Baena and colleagues recently reported the results from their 15-year study of a Colombian kindred affected by the E280A *PSEN1* mutation [4]. Of 1,784 family members enrolled, 1,181 were genotyped yielding 459 carriers and 722 noncarriers. Of the carriers, 449 had undergone neuropsychological testing; 140 (31%) were assessed only once, whilst the remainder had serial assessments (average 3.2 assessments, range 1 to 12) at intervals ranging from 1 to 11 years (mean 2.1 years). The neuropsychological data from 499 of the noncarriers were used to generate normal parameters for the Colombian population under the age of 50, which were grouped according to age and education.

The authors defined five clinical states: healthy, dementia, and three intermediate stages of pre-dementia cognitive impairment [4]. Pre-dementia cognitive impairment was defined as a score 2 standard deviations away from the noncarrier mean, adjusted for age and education, on at least one cognitive test. Those patients with pre-dementia cognitive impairment but no memory complaints were defined as asymptomatic pre-mild cognitive impairment (pre-MCI). Those patients with memory complaints and a score higher than the noncarrier mean on a subjective memory complaints checklist, but with little or no impairment of complex activities of daily living (ADL), were defined as MCI. In between, a stage of symptomatic pre-MCI defined those individuals who had some memory complaints but did not score higher than the noncarrier mean on the subjective memory complaints checklist, with preserved ADL. Individuals with memory complaints interfering with complex and basic ADL were defined as demented. Using survival analyses to model progression, the authors described a typical trajectory from healthy to asymptomatic pre-MCI (median age at onset 35 years), to symptomatic pre-MCI (median age 38 years), to MCI (median age 44 years), to dementia (median age 49 years) and ultimately to death (median age 59 years). The cognitive

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profile was predominantly amnestic, with some transient recovery noted in the symptomatic pre-MCI stage, followed by a continuous decline in multiple cognitive domains.

Given the phenotypic heterogeneity observed between different genetic mutations associated with familial AD [5], Acosta-Baena and colleagues' study of such a large number of individuals with the same mutation is a valuable addition to the literature. Their framework for characterising the pre-dementia stages of familial AD does raise certain issues, however, which question how applicable it may be to other populations with familial AD and highlight the difficulties of defining pre-dementia clinical stages.

As the authors discuss, the concept of MCI was not widespread when they started their study and debate continues regarding how MCI may best be defined. Their MCI definition resembles the Petersen criteria, which require the presence of memory complaints with preserved basic ADL and no or minimal impairment of complex ADL [6]. While the Petersen criterion for cognitive impairment is a score 1.5 standard deviations away from normal values on neuropsychological tests, however, Acosta-Baena and colleagues defined impairment as 2 standard deviations away. They chose this more stringent cut-off value to reduce the possibility of false positives; a valid justification, although it limits how comparable their results are with studies employing the Petersen criteria.

Comparability within the field is further limited by the fact that many other studies do not incorporate neuropsychological results into their classification of MCI, instead defining it as a score of 0.5 on the clinical dementia rating scale; a structured interview with the participant and a close informant [7]. As the field moves forward and prevention trials for familial AD are launched, it will be crucial that different studies share a common construct of MCI if the efficacies of different therapies are to be compared.

The situation is more complex regarding the term pre-MCI, which is conventionally used to describe subjective memory complaints without evidence of neuropsychological deficit [8]. Acosta-Baena and colleagues, however, use the term pre-MCI for individuals with objective cognitive impairment who are either asymptomatic or symptomatic with a score on the subjective memory complaints checklist lower than the noncarrier mean. In some centres this symptomatic pre-MCI group would have been classified as MCI, and the findings by the authors of some transient recovery in the symptomatic pre-MCI group may be akin to the subset of MCI patients in other studies whose symptoms revert.

The authors speculate that cognitive reserve is the source of the transient recovery in these individuals; although an alternative explanation may be that anxiety or depression was the cause of the initial symptoms. It is not unusual for individuals at risk of familial AD to experience considerable anxiety about the possibility of developing memory problems, which understandably accentuates as they grow close to the age at which their parent developed symptoms. The authors' reference to the subjective memory complaints scores in the non-carriers provided one way of addressing this issue, but it would have also been interesting to know how the individuals with symptomatic pre-MCI who improved scored on the geriatric depression scale.

It is notable that all of the symptomatic participants in Acosta-Baena and colleagues' study had objective cognitive deficits by the time they manifested symptoms. In our experience, not all individuals who develop familial AD follow the same trajectory. Whilst objective cognitive deficits do manifest several years prior to symptoms in many patients [9], others may develop memory complaints without objective impairment initially, and would conform to the conventional definition of pre-MCI. Anxiety may play a role in these symptoms, or it may be that standard neuropsychological tests are not sensitive enough to detect the earliest deficits in highly educated participants. The low education level in the current study (>50% had <6 years of education) may limit the generalisability of the results to other populations affected by familial AD. One must also be wary of practice effects in individuals who have been participating in natural history studies for many years. All of these factors should be considered as limitations when using neuropsychological tests as the basis for defining stages of disease.

Much progress has been made to refine and incorporate biomarkers into definitions of pre-dementia stages in sporadic AD [10-12]. Understanding the sequence of biomarker changes in familial AD may, in time, contribute to the characterisation of stages of disease. However, as biomarker abnormalities are already present in pre-symptomatic familial AD [13-15], the interpretation of their significance itself requires correlation with clinical stage. How these stages are defined will be influenced by the meaning that symptoms have for an individual, their family and sociocultural environment. Variability in these factors across different geographical locations brings challenges, but the rarity of familial AD means that efforts to prevent it must take a global perspective and start by establishing a common framework for defining the stages of disease.

Abbreviations

AD, Alzheimer's disease; ADL, activities of daily living; MCI, mild cognitive impairment.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements
The present work was undertaken at UCLH/UCL, who received a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research UK Co-ordinating Centre and has also received equipment funded by Alzheimer's Research UK. NSR is supported by a Medical Research Council (UK) Clinical Research Training Fellowship. MNR is a NIHR Senior Investigator and a site Principal Investigator for the National Institute on Aging-funded DIAN (Dominantly Inherited Alzheimer Network) study, which receives additional support from DeNDRON, the NIHR clinical research network for dementia and neurodegenerative diseases.

Published: 27 September 2011

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doi:10.1186/alzrt91
Cite this article as: Ryan NS, Rossor MN: **Defining and describing the pre-dementia stages of familial Alzheimer's disease.** *Alzheimer's Research & Therapy* 2011, **3:**29.