The Natural History of Alzheimer Disease

A Longitudinal Presymptomatic and Symptomatic Study of a Familial Cohort

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Background: Knowledge of the evolution of cognitive deficits in Alzheimer disease is important for our understanding of disease progression. Previous reports, however, have either lacked detail or have not covered the presymptomatic stages.

Objective: To delineate the onset and progression of clinical and neuropsychological abnormalities in familial Alzheimer disease.

Methods: Nineteen subjects with familial Alzheimer disease underwent serial clinical and neuropsychological assessments. Eight of these had undergone presymptomatic assessments. The follow-up period was 1 to 10 years (mean, 5 years). The relative timing of the occurrence of 3 markers of disease onset and progression (onset of symptoms, Mini-Mental State Examination score $\leq 24$, and impaired scores on a range of neuropsychological tests) were compared using the binomial exact test.

Results: Neurological abnormalities were not prominent, although myoclonus appeared early in some. Mini-Mental State Examination score was not sensitive to early disease. Memory and general intelligence deficits appeared at an earlier stage, in some patients when presymptomatic. Perceptual, naming, and especially spelling skills were preserved to a late stage.

Conclusion: Familial Alzheimer disease may have a long prodromal phase of several years with subtle deficits initially of general intelligence and memory, while spelling, naming, and perception are relatively preserved until a late stage.

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A detailed understanding of the clinical and neuropsychological features of Alzheimer disease (AD) is essential for improving the accuracy of diagnosis and prognosis and the assessment of potential disease-modifying treatments of the future. The typical early, insidious decline in episodic memory is well established, but surprisingly little has been reported of the subsequent pattern of progression of neuropsychological and clinical features. Most studies have been cross-sectional, and those longitudinal studies that have been performed have focused on rates of progression rather than on how the pattern of decline in 1 specific cognitive domain relates to that in another.

One reason for the limited study of this area is the difficulty in confident diagnosis of AD, especially at the early stages in which deficits in specific cognitive domains are of most interest. The occurrence of AD in an early-onset, autosomally dominantly inherited familial form provides an opportunity to study patients in whom early diagnosis can be made confidently and in whom, unlike in elderly populations, comorbidity is seldom a significant consideration.

Previous studies of familial AD (FAD) have either focused on reporting the earliest features of the disease or on progression in those already moderately affected. The course and pattern of cognitive decline from the presymptomatic stages to advanced disease have not been systematically reported in detail.

Methods

Patients with autosomal dominant, early-onset FAD were recruited into a longitudinal study from referrals to the Dementia Research Group at The National Hospital for Neurology and Neurosurgery, London, England. The study received ethical approval from the institutional review board and informed consent was obtained. All families of patients included fulfilled 3 generational criteria for au-
tosomal dominant inheritance, and at least 1 affected member of each family had undergone neuropathological examination. All patients, on completion of this study, fulfilled standard criteria for probable AD (except for the requirement of the criteria of the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations that symptoms develop at older than 40 years). For patients who had participated in a longitudinal study of subjects at risk of FAD prior to developing the disease, presymptomatic data were included.

Each patient had serial clinical and neuropsychological assessments at the National Hospital for Neurology and Neurosurgery at approximately annual intervals, until untestable. Assessors were blinded to the outcome of assessments other than their own.

Clinical assessment included history taking, neurological examination, and Mini-Mental State Examination (MMSE). Onset of symptoms was established from information given by the patient and their caregiver when the patient was first symptomatic.

Neuropsychological tests assessed intellectual functioning, current (Wechsler Adult Intelligence Scale Revised) and premorbid (National Adult Reading Test) verbal and visual recognition memory (Recognition Memory Test for Words and Faces), naming (Graded Naming Test), spelling (Oral Graded Spelling Test), calculation (Graded Difficulty Spelling Test), and visuospatial and perceptual abilities (cube rotation pedigrees, with 8 and 10; calculation (Graded Difficulty Spelling Test); and recognition memory (Recognition Memory Test for Words and Faces)).

For all cognitive domains except intelligence, raw scores were converted into percentiles, referring to published normative data. Scores at or below the fifth percentile were taken to indicate an impairment. For intelligence, a difference of 10 or greater was considered an impairment.

The relative timings of the onset of symptoms, impaired scores on the MMSE (≤24), and impairments in the different cognitive domains were analyzed in a pairwise fashion, using the binomial exact test. In some patients, performance was impaired but then reverted to normal before declining again. We determined the time of onset to be when a deficit was first observed but also repeated the analysis taking the time of onset to be when a deficit first became permanent.

Modified Kaplan-Meier plots were used to illustrate the relative survival of cognitive domains and unimpaired MMSE scores across time following the onset of symptoms. The proportion plotted at time zero represents those patients who were symptomatic before the onset of symptoms and were unimpaired. Drops in the proportion represent those patients who first showed a deficit at the given assessment time. The number of patients who had had an initial assessment but did not show a deficit prior to this time was used as the denominator.

RESULTS

Nineteen patients participated (9 male). Seven patients belonged to amyloid precursor protein (APP) gene mutation pedigrees, with V717G (3 patients), V717I (3 patients), and V717L (1 patient) mutations. Eleven patients belonged to presenilin-1 (PSEN1) gene mutation pedigrees, 8 with point mutations (G378V, M139V, H143F, or L153V) and 3 with deletions (Δ4 or 9). One patient belonged to a pedigree in which we have not been able to demonstrate a mutation in APP, PSEN1, or presenilin-2.

Mean age at onset of symptoms was 44 years (range, 35-57 years) and at first assessment when symptomatic was 46 years (range, 35-59 years). At the time of last contact with the research team, 6 patients had died (mean, 8.2 years after onset of symptoms [range, 5.6-12.7 years]), 10 patients were living at home (mean, 7.3 years after onset [range, 2.7-12.4 years]), and 3 patients were in residential care (mean, 8.9 years after onset [range, 7.0-11.2 years]).

NEUROLOGICAL FEATURES

Clinical data were available for 18 subjects. Fifteen developed abnormalities on neurological examination during the study, as follows: myoclonus (11 subjects), a mean of 4 years (range, 1-11 years) after symptom onset; limb dyspraxia (8); brisk reflexes (4); late visual disorientation (3); and nonspecifically slow gait (3). Two subjects developed seizures during study follow-up, 5 and 6 years after symptom onset, respectively, and seizures occurred in a further subject after follow-up ceased, 6 months prior to death.

NEUROPSYCHOLOGICAL FEATURES

All 19 patients underwent at least 2 neuropsychological assessments a minimum of 1 year apart (mean, 5.4 assessments [range, 2-14 assessments]). Mean interval between assessments was 1 year, with a mean follow-up of 5 years (range, 1-10 years). Sixteen patients were untestable at the end of the study. Mean time from onset of symptoms to final neuropsychological assessment in these 16 patients was 5 years (range, 1-10 years). Three patients are receiving ongoing follow-up.

Eight patients had presymptomatic neuropsychological assessments at least 6 months before reported onset of symptoms (starting a mean of 2.7 years [range, 0.8-5.0 years] before onset of symptoms; mean age of 42 years [range, 31-50 years]). One further subject was first assessed only 2 months before developing symptoms. All subjects had subsequent symptomatic assessments.

Table 1 presents the proportion of patients who showed a deficit in each domain at initial and final presymptomatic assessment and initial and final symptomatic assessment. At initial presymptomatic assessment, impairments of cognition were restricted to general intelligence (4/8) and memory (2/8). By the final presymptomatic assessment, 5 of 9 of those assessed showed deficits in general intelligence, 3 of 9 in visual memory, and 2 of 9 in verbal memory, whereas none showed deficits in MMSE score. At the first symptomatic assessment, only 4 of 11 patients showed deficits in MMSE score. However, 14 of 19 showed deficits in intelligence, 14 of 18 in verbal memory, and 11 of 18 in visual memory; 5 of 17 were dyscalculic. Disorders of perception, naming, and spelling were rare. By the time of the final symptomatic assessment, cognitive deficits were pervasive with relative preservation of naming and perception (consistent with previous reports). Spelling skills were especially resilient.

Figure 1 illustrates the typical ordering of deficits occurring in the different domains. Domains placed toward the left of the diagram generally show deficits at earlier points than domains placed further toward the right. When there is no dashed circle/oval enclosing a pair

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of domains, the relative order of deficits occurring achieves statistical significance. The statistical details of this are shown in **Table 2**. Mini-Mental State Examination score, calculation, visuoperceptual and visuospatial skills, naming, and spelling all showed deficits significantly later than symptom onset and in the order shown in Figure 1. When the data were reanalyzed using the time when deficits first became permanent (rather than sometimes showing transient improvement), verbal IQ and visual memory also showed deficits significantly later than symptom onset, but there were no other differences. **Figure 2** shows the modified Kaplan-Meier plots for survival of each domain, for visual comparison.

**CORRELATION OF NEUROLOGICAL ABNORMALITIES AND MEMORY DEFICITS**

Five patients were examined when presymptomatic and when memory scores were normal. Four had subtle abnormalities at this early stage: myoclonus (3) and tremor (1).

At the time of first memory impairment, 14 patients had a neurological examination. Seven had subtle abnormalities: myoclonus (5), dyspraxia (1), pout reflex (1), and broken pursuit eye movements (1).

This study provides detailed longitudinal data across a prolonged follow-up period of up to 10 years of the neuropsychological and clinical features of FAD. Our subjects carried a range of pathogenic APP and PSEN1 mutations and belonged to well-characterized FAD pedigrees. The inclusion of presymptomatic assessments and the long follow-up allowed an evaluation of the deficits across much of the disease course of FAD.

It is seldom possible to date symptom onset more accurately than half a year, and data should be interpreted in light of this. Initial symptoms begin very insidiously, sometimes across a period of several years before the subject seeks medical attention and meets accepted criteria for the diagnosis of AD. It is also recognized that histo-
Table 2. Order of Development of Deficits in Different Psychometric Domains and Time of Disease Onset: Pairwise Comparisons

<table>
<thead>
<tr>
<th>Onset</th>
<th>RMT-W</th>
<th>RMT-F</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>MMSE</th>
<th>Calculation</th>
<th>Visuospatial</th>
<th>Visuoperception</th>
<th>Naming</th>
<th>Spelling</th>
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Abbreviations: MMSE, Mini-Mental State Examination; RMT-F, Recognition Memory Test–Faces; RMT-W, Recognition Memory Test–Words.

*Values are expressed as the P value (from the binomial exact test) followed by the number of patients where the domain named in the row heading shows a deficit first followed by the number of patients where the domain named in the column heading shows a deficit first. Where the P value reached statistical significance (P < .05), the name of the domain with the earlier deficit also appears in the relevant cell. Patients where both domains show a deficit together or not at all or where missing values meant the order could not be determined were excluded. Onset is defined as the clinical onset of disease as estimated by year of initial symptoms.

The length of the disease course was very similar to that reported in sporadic AD. Myoclonus in FAD may begin early, at or before the time of first objective memory impairment, though it was not prominent. Familial AD may have a long prodrome during which cognitive deficits are subtle and may be initially limited to general intelligence and memory. Spelling was the most resilient cognitive domain, and naming and perception were also preserved to a late stage.

CONCLUSIONS

The celebrity pathological change may have begun even earlier, some years before symptom onset.6,16

Abnormalities of the neurological examination were not prominent, though myoclonus was noted at or before the time of the first objective impairment of memory in some. This was usually fine finger myoclonus and may not have been apparent to a casual observer. Of note, patients and their spouses did not comment on myoclonus at this early stage.

Our study, in line with previously reported data,3 indicated early impairment of episodic memory and general intelligence in FAD. Formal neuropsychological assessment was essential for the detection of these early cognitive changes. As expected, the MMSE was less sensitive than these measures, though performed reasonably well in detecting impairment before more widespread cognitive deficits were present. In terms of early diagnosis, however, it was limited, with 50% of patients still scoring higher than the cutoff score of 24 of 30 nearly 4 years after onset of symptoms.

Previous cross-sectional studies have reached contradictory conclusions about the timing of occurrence of naming deficits. Ardila et al8 reported naming difficulties in their poorly educated subjects without dementia who carried a mutation. However, Warrington et al15 reported relatively preserved naming in FAD compared with sporadic AD. Our data show that naming is frequently preserved many years after initial symptoms and also document that perception is a relatively resistant cognitive skill in FAD. The very late preservation of spelling is remarkable, presenting an island of preserved cognitive function when subjects were moderately or severely affected.

Familial AD is often said to follow a more aggressive disease course than sporadic AD. This is not supported by our data; 6 cases (5 alive at last contact) are so far known to have lived for more than 10 years. Survival compares favorably with that in later-onset sporadic AD.17

CONCLUSIONS
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Author Contributions: Study concept and design: Cipolotti, Fox, Janssen, and Rossor. Acquisition of data: Godbolt, Cipolotti, Fox, and Janssen. Analysis and interpretation of data: Godbolt, Cipolotti, Watt, Fox, and Rossor. Drafting of the manuscript: Godbolt, Cipolotti, Watt, Fox, and Janssen. Critical revision of the manuscript for important intellectual content: Godbolt, Cipolotti, Watt, Fox, Janssen, and Rossor. Statistical analysis: Watt. Obtained funding: Cipolotti and Rossor. Administrative, technical, and material support: Janssen. Study supervision: Cipolotti, Fox, and Rossor.

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ARCHIVES Express

The ARCHIVES launched a new ARCHIVES Express section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited ARCHIVES Express review. We look forward to publishing your important new research in this accelerated manner.

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