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Primary Degenerative Mild Cognitive Impairment: Study Population, Clinical, Brain Imaging and Biochemical Findings

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Key Words
Mild cognitive impairment · Alzheimer's disease · Diagnostic markers

Abstract
Mild cognitive impairment (MCI) is a heterogeneous clinical syndrome for which no international diagnostic criteria have yet been established. Longitudinal studies have shown that many individuals who later develop dementia pass through a stage of MCI. We are following up 36 individuals who were initially diagnosed as having the memory-impaired primary degenerative type of MCI and therefore are at high risk of developing Alzheimer's disease. Clinical, neuropsychological, brain imaging and CSF biochemical markers were examined. Findings were remarkably heterogeneous even in this highly selected group of patients. This suggests that MCI is aetiologically not uniform.

Introduction

Alzheimer's disease (AD), frontotemporal degeneration and Lewy body disease are prevalent neurodegenerative disorders which cause severe cognitive decline and profound disability in the later stages of their course. Current criteria link the clinical diagnosis of AD, frontotemporal degeneration and Lewy body disease to the presence of dementia. This syndrome is characterised by deterioration from premorbid levels in multiple cognitive domains including memory of sufficient severity to interfere significantly with activities of daily living. Degenerative dementias, however, are typically preceded by uncharacteristic states of poor memory and concentration, irritability and fatigue, or by subtle changes in personality, social conduct and emotional control [1]. The concept of prodromal dementia has been rediscovered in recent years in studies investigating the border zone between normal ageing and mild dementia. For this border zone a variety of terms and definitions have been proposed, including 'age-consistent memory impairment', 'age-associated memory impairment' (AAMI) [2], 'late-life forgetfulness' [3], 'aging-associated cognitive decline' (AACD) [4], 'dysmentia' [5], 'cognitively impaired not demented' (CIND) [6], 'memory-impaired non-demented' [7] and 'mild cognitive impairment' (MCI) [8]. These definitions have in

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common a performance below the age norm on tests of memory (MCI) and/or other cognitive domains (AAMI, AACD, CIND) with preserved general intellectual function, normal activities of daily living and a score of 0.5 on the Clinical Dementia Rating (CDR) scale [9, 10]. Follow-up studies have consistently demonstrated that patients with MCI go on to develop dementia at a rate of approximately 15% per year [11]. At autopsy, MCI subjects show a spectrum of pathology including AD, Parkinson's disease, vascular changes and hippocampal sclerosis [12, 13]. Taken together this evidence suggests that a substantial part of MCI represents prodromal dementia. The study of MCI subjects can therefore provide insight into the early stages of neurodegenerative disorders which until recently have escaped clinical diagnosis. In the present paper we describe a group of patients with primary degenerative MCI whom we are following up prospectively to confirm the diagnosis and to determine the prognostic value of neuropsychological, biochemical, brain imaging and genetic markers in MCI.

Materials and Methods

Patients

In January 1998, we initiated a follow-up study of primary degenerative MCI. To define the patient sample we applied the Mayo Clinic criteria [14] which require subjective complaints of defective memory, normal activities of daily living, normal general cognitive functioning, abnormal memory for age as demonstrated by a performance of at least 1.5 standard deviations (SD) below the age norm on the CERAD-NP delayed verbal recall (see below), absence of dementia, and a CDR of 0.5. Patients were only included if an informant was willing to participate in the follow-up protocol which consisted of annual visits to the clinic and additional telephone interviews every 6 months.

We excluded patients with delirious states and with any intracerebral or systemic disorder which could account for the cognitive impairment. Specifically, patients with significant cerebrovascular pathology (more than 2 lacunes, 1 lacune in a strategic location, large or multiple cortical infarctions, severe white matter change) were not enrolled. We also excluded patients who were on regular medication with acetylcholinesterase inhibitors, since this class of drugs is currently investigated for its potential to slow down the progression of symptoms in MCI. In this way we narrowed down MCI to a memory-impaired neurodegenerative subtype.

Recruitment

Over the past few years the number of patients diagnosed as having MCI at our memory clinic had been 20 per year. We tried to increase the number of potential participants by various measures. Seminars were held for general practitioners, neurologists and psychiatrists in October 1998 and March 1999, featuring diagnosis and treatment of MCI. The diagnostic and follow-up programme was announced in an article on AD research which appeared in a national weekly newspaper. Moreover, the programme was highlighted in three television broadcasts on AD in February and March 1999.

Diagnostic Procedures and Assessment Instruments

Patients were examined at a university out-patient unit for cognitive disorders. They underwent a standardised diagnostic procedure which included the following components: history from the patient and from an informant; medical, neurological and psychiatric examinations; cognitive assessment using the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP); assessment of severity using the CDR; assessment of depression using the Geriatric Depression Scale (GDS); cranial magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET); laboratory screening and apolipoprotein E (ApoE) genotyping; lumbar puncture for cerebrospinal fluid (CSF) Aβ(1–42) protein and tau measurement.

The age at onset was defined as the age when first evidence of memory deficit was noticed either by the patient or by the informant. Formal education was defined as the cumulative years of school and years of apprenticeship, technical school, college or university.

The CERAD-NP [15–18] includes a measure of category fluency, a modified Boston Naming Test, the Mini Mental State Examination (MMSE), a word list learning, memory and recognition procedure and an assessment of constructional praxis. We used an authorised German version for which normative data are available [19, 20]. The clock-drawing test was scored from 1 (perfect) to 6 (unrecognisable) [21]. The CDR [9, 10] was completed after interviewing the patient and the informant. The sum of the boxes (CDR-SB) was calculated by summing up the box scores for each patient. The GDS 15-item version [22, 23] is a self-rating screening instrument for depression in the elderly population. A score of <5 indicates the absence of clinically significant depressive symptoms, a score of >10 indicates the presence of a severe depressive episode [24].

The routine laboratory included a chemistry group, complete blood cell count, blood glucose, vitamin B_{12} and folic acid levels, basic thyroid hormone level, syphilis serological testing and Lyme borreliosis serological testing.

ApoE genotypes were determined by hybridisation of the amplified biotinylated product with allele-specific oligonucleotides immobilised on membrane strips followed by chromogen detection (Inno-Lipa ApoE, Innogenetics, Zwijndrecht, Belgium).

CSF (5–8 ml) was collected in sterile polypropylene tubes using atraumatic cannulas placed in the intervertebral space L_3/L_4 or L_4/L_5 and was shipped on ice. Serum and EDTA plasma were obtained by venous puncture. CSF was centrifuged for 10 min at 4,000 *g*. The remaining CSF supernatants were aliquoted and immediately frozen for later tau and Aβ(1–42) determination. EDTA plasma was also frozen for later DNA extraction.

The total tau protein content was measured in duplicate by an enzyme-linked immuno-assay (ELISA) as described elsewhere [25] (Innogenetics; kit No. K-1032). Measurement of CSF Aβ(1–42) protein was performed in duplicate by ELISA as described elsewhere [26].

Cranial MRI was conducted on an open 0.2-tesla Siemens magnetome. The standardised protocol included a sagittal T_1-weighted flair image using a three-dimensional gradient echo technique with 40 contiguous partitions and 4 mm effective slice thickness, a coronal T_1-weighted turbo inversion recovery sequence perpendicular to the long axis of the hippocampus with 2×15 slices and slice thickness of 3 mm, and an axial T_2-weighted turbo spin echo sequence in AC-PC

Table 1. Demographic data (means ± SD)

Variable	Males (n = 21)	Females (n = 15)	Total (n = 36)
Age, years	67.5 ± 9.3	71.1 ± 8.2	69.0 ± 9.0
Age at onset, years	64.2 ± 9.3	69.2 ± 8.5	66.3 ± 9.3
Education, years	14.5 ± 2.7	11.2 ± 2.3	13.1 ± 3.0
Family history of dementia	13 (61.9%)	10 (66.7%)	23 (63.9%)

alignment with 19 slices and a slice thickness of 6 mm. MR images were evluated by visual inspection by an experienced senior neuroradiologist. Volumetric analysis of MR data was also performed and will be reported separately.

All patients underwent ^{18}F-FDG PET imaging. Under standard resting conditions (eyes closed in dimmed ambient light) 370 MB ^{18}F-FDG was injected at rest and 30 min later PET imaging was performed using a Siemens 951 R/31 PET scanner (CTI, Knoxville, Tenn., USA, 3 frames of 10 min, two-dimensional mode). Attenuation correction was carried out by a standard ellipse-fitting method. PET images were analysed using an automated routine (Neurostat, University of Michigan, Ann Arbor, Mich., USA) generating standardised three-dimensional stereotactic surface projections and Z score images (individual pixelwise comparison to a database of age-matched controls). This routine has been extensively described in previous publications and has been evaluated for clinical and scientific use in patients with dementing disorders and epilepsy [27, 28].

Results

Sources of Referral

Recruitment of patients for the present study was more difficult and took longer than we had expected. Patients who experience minor cognitive impairment were reluctant to disclose the problem to general physicians, neurologists or psychiatrists. Most felt embarrassed or feared to be labelled as hypochondriac. Some recalled that their general practitioner had shown no interest in their memory complaint previously or had considered it to be a consequence of age which requires no medical attention. Using the different ways of enhancing recruitment mentioned above, 25% of the patients were referred by general practitioners, 36% were sent in by psychiatrists or neurologists, 14% came from other clinics and 25% were self-referred.

Demographic Data

At the time of writing, 36 patients (21 males, 15 females) had been enrolled. Demographic details are presented in table 1. Seventy-five percent of the patients were married, 19% were widowed, and a minority were divorced or single. The average years of formal education were 14.5 ± 2.7.

Ten patients had a university degree, 8 were employees, 7 craftsmen, 5 had social occupations, 2 were army officers and 4 were housewives. At entry in the study, 30 (83%) patients were retired while 6 (17%) were still at work. Surprisingly, almost two thirds of the patients had a positive family history of dementia. In half of these cases first-degree relatives were affected, most frequently mothers (30.6%). In 6 patients second-degree relatives were or had been demented.

In 11% of the sample, both first- and second-degree relatives were affected, and in 25% of the patients more than one family member had or had had dementia. By comparison, the frequency of a positive family history of dementia is only 35% in AD patients who are consecutively seen at the same out-patient unit [29].

Subjective Complaints

Without exception, patients were prompted to seek diagnostic evaluation by memory problems. Most were alerted by dementia occurring in family members. This probably explains the high rate of positive family histories. All patients complained of memory problems with gradual onset. Frequent examples were searching for things in the house, forgetting names, forgetting telephone numbers or appointments and forgetting more rapidly the content of written texts. Some patients felt they were impaired in their ability to perform more than one task at one time. Others also reported minor word finding difficulty or problems with temporal orientation.

Informants' Observations

The informants confirmed the patients' complaints of defective memory in every case. According to their experience the most frequent evidence of defective memory was inability to recall recent events such as conversations, television shows, newspaper articles, book chapters or appointments. Other examples were forgetting telephone numbers, searching for misplaced objects, and failure to take medications regularly. Informants also reported that the patients had difficulty acquiring new material. Non-

Table 2. Cognitive symptoms

CERAD-NP domain	>1.5 SD below age norm	
	n	%
Delayed word recall	36	100
Immediate word recall	25	69
Verbal recognition	19	53
Non-verbal delayed recall	10	28
Category fluency	9	25
Object naming	9	25
Constructional praxis	3	8
MMSE	28	78

Table 3. Findings in PET

Pattern	Frequency	
	n	%
Significant hypometabolism in AD-typical region	7	19
Hypometabolism in posterior cingulate region	6	17
Non-significant hypometabolism in AD-typical regions	6	17
Multifocal metabolic reduction	2	6
Frontal hypometabolism	3	8
No metabolic abnormalities	12	33

memory cognitive problems were also reported, including impaired word finding, slowing of speech, poor concentration, reduced ability to carry out multiple tasks simultaneously, difficulty with temporal relationships or topographical orientation in unfamiliar surroundings, diminished interest in social interaction and loss of drive.

Some said that patients felt distressed when they noticed their memory impairment. While denial of memory difficulty was never observed, some informants had noted avoidance of challenging situations.

Medication and Physical Health

At the time of diagnostic evaluation the majority of patients did not receive any medication for their memory problem. On the other hand, 36% of the patients were on regular nootropic medication, and 14% were taking antidepressants. *Ginkgo biloba* accounted for one half of nootropic prescriptions. No patient was under neuroleptic treatment. The most frequent somatic diseases were hypertension (35%), cardiac disease (22%), hyperlipidaemia (17%) and thyroid disorder (8%). There were no laboratory abnormalities that could be considered as a cause of the cognitive impairment. The normal ranges for vitamin B_{12} and folic acid in our laboratory are 200–950 pg/ml and 3–17 ng/ml, respectively. Patients had a mean level of 351 pg/ml for vitamin B_{12} and of 7.0 ng/ml for folic acid. In 2 patients only vitamin B_{12} (175 and 195 pg/ml) and in 1 patient folic acid (2.5 ng/l) was slightly subnormal.

Cognitive Symptoms

As required by the inclusion criteria applied, all patients had a memory performance at least 1.5 SD below their age norm on the CERAD-NP delayed verbal recall test. Most subjects also showed subnormal results in other memory-related tasks including immediate verbal recall and delayed verbal recognition (table 2). Delayed non-verbal recall, however, was within normal limits in most patients. On the MMSE the mean was 27.2 ± 1.7 points and the majority scored more than 1.5 SD lower than their cognitively healthy age peers. In most patients cognitive performance was normal for age in non-memory cognitive domains including category fluency, object naming and visuoconstruction.

Patients who showed impaired function in these cognitive domains were also more impaired in activities of daily living than the remaining subjects. On the clock-drawing test, the majority of patients (72%) were able to draw a perfect clockface and to set the hands correctly. Nineteen percent had a score of 3 which indicates mild to moderate visuoconstructional impairment. The mean CDR-SB score was 2.08 ± 0.95.

Non-Cognitive Symptoms

According to patients' and informants' reports non-cognitive symptoms were rare. The average score on the GDS was 3.8 ± 2.0. Most patients said they were concerned about their memory problems and were worried about the future. Some reported nervousness, verbal aggression or short temper in situations when their memory deficits became obvious to others.

Magnetic Resonance Imaging

In 64% of patients the MR scan was normal for age. Temporal lobe atrophy in excess of age-associated changes was seen in 28% of the patients. Eight percent showed global cortical atrophy with ventricular enlargement. One patient had frontoparietal atrophy. Seven patients showed moderate leukoaraiosis and another 7 had minor lacunar infarctions.

Positron Emission Tomography

Seven patients (19%) showed significant metabolic reductions in the temporal, parietal and frontal lobes as well as in the posterior cingulate region. This pattern is consistent with early AD (table 3). Isolated hypometabolism in the posterior cingulum was seen in 6 patients (17%). This pattern of metabolic deficits has previously been found in patients with incipient AD. Another 7 patients (19%) showed metabolic reductions in AD-typical cortical areas but these were not significant. Two patients had multifocal abnormalities suggestive of ischaemic lesions. Three subjects showed metabolic reduction in the frontal lobes only. The PET scan was normal in a minority of 12 patients. Altogether, 13 patients (36%) had metabolic changes in the PET scan that were consistent with incipient AD.

ApoE Genotypes and Allele Frequency

The allele frequencies were 0.06, 0.58 and 0.36 for the ε2, ε3 and ε4 alleles, respectively. More than half (53%) of the MCI patients were carriers of the ApoE ε4 allele. Seven subjects (19%) were homozygous for ε4. Only 4 (11%) patients carried one ε2 allele, 14 (39%) were homozygous for ε3.

CSF Markers

In a recent multicentre study optimal cut-off values for biochemical markers in the CSF have been determined for the discrimination between AD and normal ageing [26]. Using these cut-off values [252 ng/l for tau and 643 ng/l for Aβ(1–42)], 19 MCI patients (53%) showed elevated tau protein levels and 24 (67%) had reduced Aβ(1–42) protein concentrations.

Combination of Biological Markers

Of the putative markers of AD examined [temporal lobe atrophy on MRI, temporoparietal hypometabolism on PET, high CSF tau, low CSF Aβ(1–42) protein] all 4 were jointly present in 4 (11%) patients. Three markers were combined in 11 (31%) of the patients, 2 markers were positive in 10 (28%), and at least 1 marker was present in 7 (19%). In 4 (11%) all 4 markers were negative.

Disclosure of Diagnosis and Treatment Suggestions

The patients were informed that no underlying cause was found which might explain their memory problem and that their condition was currently referred to as MCI. Patients were also told that although they had an increased risk of developing dementia, current medical knowledge allowed no individual prognosis. Invariably, patients expressed their relief over not being diagnosed as having AD, although the majority were concerned about the future. Some patients with a positive family history of dementia worried about their genetic risk. All were interested in medications that might improve their memory problem or at least prevent worsening. Vitamin E (800 IU/day) in combination with vitamin C was suggested as a potentially neuroprotective agent and piracetam (2.4 g/day) was proposed as a well-tolerated cognition enhancer. Patients with a vitamin B_{12} level and/or a folic acid level in the lower normal range given by our laboratory might also benefit from a substitution with vitamin B_{12} and folic acid.

Discussion

In the present study we examined a group of patients with a primary degenerative amnesic type of MCI. To select this population we applied the Mayo Clinic criteria for MCI [14] in conjunction with the exclusion criteria that are used to define probable AD [30].

Patients were included who complained about memory problems in the presence of otherwise normal cognitive functioning, had preserved basic activities of daily living and who were rated stage 0.5 on the CDR. Subjects with non-organic psychiatric disorders or with physical conditions which might explain the cognitive impairment, were not enrolled.

In particular, cerebrovascular changes which are listed as potential causes of dementia in the NINDS-AIREN criteria [31] were also excluded. Therefore, the memory problems observed in these patients, who show a progression of symptoms over time, are most likely caused by primary degenerative brain diseases including AD, frontotemporal degeneration and Lewy body disease.

In most instances, the patient's presentation at our research out-patient unit was driven by a positive family history of dementia and by the concern of carrying a genetic risk. As a consequence of the recruitment and selection process, the subjects of the present study were highly educated, and 53% were carriers of the ApoE ε4 allele. This allele frequency is even higher than that of unselected AD patients seen at the same out-patient unit (43%) and reflects the special ascertainment of these study individuals with their high rate of a positive family history. The ε4 allele frequency observed in cognitively healthy elderly controls (11%), collected at the same site [32] is quite different. Compared to AD samples, the majority of the par-

ticipants of the present study were fairly young, and many were working at the time of presentation. They were fully aware of a decrease in cognitive ability relative to the previous level of functioning. Also, they had noticed the cognitive decline before it became apparent to relatives or friends. This suggests that in highly educated and relatively young individuals self-reported cognitive decline may be a more valid indicator of incipient organic brain disorders than in an elderly and less educated individual where such complaints often point to depression.

Although most causes of cognitive impairment other than neurodegenerative diseases were excluded and the spectrum of clinical severity was very narrow, the patient population was remarkably heterogeneous with respect to clinical, neuro-imaging and biochemical findings.

Isolated memory problems which are aetiologically non-specific were seen in 41.7% of the subjects, whereas the rest showed a pattern of impairment in multiple cognitive areas including mild language, orientation and visuospatial disturbances. This is suggestive of an underlying disorder leading to dementia. Whereas brain imaging (MRI and PET) was normal in 36.1% and biochemical results (tau protein and Aβ) were normal in 25.0% of the patients examined, brain imaging was clearly abnormal in 30.6% and biochemical results in 41.7%.

This heterogeneity suggested that we were either dealing with several underlying conditions which are associated with different clinical phenotypes at the clinical stage of MCI or with a single common disease entity which can have different manifestations at this degree of severity, or a mixture of both. Taking into account the relative frequency of neurodegenerative diseases in the population at the age of our sample, however, the assumption of a single common disease (AD) with large phenotypic variability is a probable but not the only explanation. At the stage of mild to moderate dementia the clinical heterogeneity of AD has been demonstrated by many studies which have looked at clinical symptoms [33] or functional brain imaging [34, 35].

At any clinical stage of AD or other neurodegenerative diseases brain imaging and biochemical abnormalities are believed to reflect the underlying pathological process. We therefore examined how CSF tau, CSF Aβ42 protein, hypometabolism on PET and regional brain atrophy on MRI were related to each other. Unexpectedly, no statistically significant associations were found between MRI, PET and the biochemical markers. This could either suggest that the four markers indicate distinct features of the pathological cascade or once again point to the aetiological heterogeneity of our patient sample.

Interestingly, the 4 patients who showed 4 positive markers were 22.2 years older (77.7 years; range 75–84 years) than the 4 patients where all markers were negative (55.7 years; range 47–63 years). This is consistent with the assumption that in the oldest participants of the study the probability that MCI is caused by AD may be particularly high.

Eleven patients were positive for 3 markers (mean age: 71.2 years) whereas 7 patients were positive for only 1 marker (mean age: 67.6 years). Comparing these two groups the major difference was neither severity nor profile of cognitive impairment but overall severity as rated on the CDR. The sum of boxes was 2.32 in patients with 3 positive markers but only 1.6 in patients with only 1 positive marker. This might indicate that individuals with 3 positive markers are at a higher risk to develop clinically diagnosable AD during follow-up. Also, the ApoE ε4 allele status differed between these two groups. Of patients with 3 positive markers 68% carried the ε4 allele whereas only 29% of those with only 1 positive marker were also positive for ε4.

Findings from prospective follow-up studies suggest that the markers used in the present study may predict progression from MCI to dementia, including the ApoE ε4 allele [36], hippocampal atrophy [37–39], glucose hypometabolism in the cingulum in PET [28], low Aβ(1–42) protein levels and high tau levels in the CSF. It is unclear, however, whether a combination of markers has a greater prognostic potential than single markers. Also, it has not been demonstrated to date that biological markers have an additional value when compared with neuropsychological test results. We hypothesize that in the present sample the patients who have 4 pathological markers and a higher mean age are particularly likely to develop dementia within the follow-up period. We are aware of the fact, however, that our patient group is highly selected and may not be representative of population-based or routine clinical samples.

To our surprise, recruiting patients with MCI was difficult. Although the frequency of MCI is estimated to be at least as high as that of dementia, patients with MCI are reluctant to see physicians for their cognitive problems. Diagnostic evaluation of their condition may provide benefit, even though there is no established treatment and many issues around the concept of MCI are still unresolved. We did not measure plasma homocysteine levels in our patients. Recent evidence from the literature, however, shows a correlation of high homocysteine levels with cognitive impairment and depression [40, 41] so that screening for the homocysteine level in patients with an MCI syndrome and a substitution with vitamin B_{12} and

folic acid in those patients showing an increased level of homocysteine could be considered an interesting new treatment approach. Most patients who participated in our study felt relieved learning that their concerns about impaired cognition were justified but a diagnosis of AD which they had been afraid of could not be made.

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