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Awareness of Deficits in Mild Cognitive Impairment and Alzheimer's Disease: Do MCI Patients Have Impaired Insight?

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Key Words
Awareness · Insight · Anosognosia · Mild cognitive impairment · Alzheimer's disease · Dementia

Abstract
In this study we investigated impaired awareness of cognitive deficits in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Very few studies have addressed this topic, and methodological inconsistencies make the comparison of previous studies difficult. From a prospective research program 36 consecutive patients with mild AD (MMSE above 19), 30 with amnesic MCI and 33 matched controls were examined. Using three methods for awareness assessment we found no significant differences in the level of awareness between MCI and AD. Both groups had impaired awareness and significant heterogeneity in the clinical presentation of awareness. The results demonstrate that subjective memory problems should not be a mandatory prerequisite in suspected dementia or MCI, which makes reports from informants together with thorough clinical interview and observation central when assessing suspected dementia disorders.

Introduction

A common observation in Alzheimer's disease (AD) is that in spite of profound cognitive dysfunction and impaired activities of daily living (ADL) many patients do not recognize these deficits. Even in the early stages of AD impaired insight is common and the level of unawareness increases with disease progression [1, 2]. Some patients acknowledge a memory problem but are unaware of the implications; others completely deny any deficits. Still others may not explicitly report impairment, but when confronted with difficult tasks may show some awareness of dysfunction. The phenomenon has been described as anosognosia, unawareness of deficits, lack of insight or imperception of disease [3]. These concepts are used synonymously in this article. Behavioral and psychiatric symptoms, e.g. mania, agitation and hallucinations, are more frequent in patients with limited awareness [4–6], and care burden becomes higher [7, 8], making assessment of insight of central importance when diagnosing and treating dementia disorders.

Mild cognitive impairment (MCI) has recently attracted much interest, and subjective complaints are considered characteristic of this syndrome according to current criteria [9, 10]. Whether subjective complaints reflect cognitive impairment in MCI needs further investigation since few studies have been published on the level of awareness in this patient group. In recently published studies on MCI lack of awareness of olfactory and functional deficits has been found to be clinically useful as an

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early diagnostic marker for conversion to AD [11, 12], and a few studies have reported that MCI patients have impaired insight in functional [13] and memory abilities [14]. Other studies have found that elderly subjects with objective memory impairment have relevant insight in their amnesic difficulties [15–17].

Anosognosia is not a unitary construct, and various approaches have been taken to develop methods for assessment of awareness. Most of these have limitations [18], and no 'gold-standard' test for examining insight exists, which complicates the comparability of different studies. Four main approaches have been taken in assessing the level of awareness: (1) evaluation by clinician (structured or unstructured) [5, 19]; (2) discrepancy scores on parallel versions of rating scales or questionnaires given to the patient and a close relative [20, 21]; (3) discrepancy scores between patient self-ratings and their scores on objective memory tests [22], and (4) a combination of the three methods [18]. Evaluation by the clinician is by far the most commonly used method for assessment of awareness, but few studies have examined if the use of additional methods provides useful information not elicited by short categorical stratifications.

The objective of the present study was to assess if patients with amnesic MCI have impaired awareness as compared to patients with mild AD and healthy subjects. The assessment was thorough including both self-report, relative's evaluation and assessment by a clinician. Further, we wished to assess the comparability of the clinician's evaluation and discrepancy scores on parallel questionnaires in the 2 patient groups.

Subjects and Methods

In this study we included 36 patients with mild AD, 30 with amnesic MCI and 33 healthy controls. Patients were consecutively recruited from a prospective research program at the Copenhagen University Hospital Memory Clinic, which is an out-patient clinic based in neurology [23]. The program consecutively included all newly referred patients, aged 60 years or above, with a score of 20 or above on the Mini-Mental State Examination (MMSE). Patients had an extensive study program including neurological and physical examination, laboratory screening tests, electrocardiography, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), psychiatric evaluation, a neuropsychological examination, and a rating of dementia using Clinical Dementia Rating (CDR). After completion of the initial study program, the multidisciplinary staff established a consensus diagnostic classification concerning cognitive profile, primary diagnosis and concomitant conditions. Exclusion criteria for this study were a history of schizophrenia, more than one episode of depression, obsessive compulsive disorder, abuse of alcohol and drugs, head trauma, or severe concomitant diseases which were found disabling for the extensive study program.

A total of 105 patients completed the study program by the end of the inclusion period for this project, and 66 met the criteria for AD or MCI. AD was defined from the NINCDS-ADRDA criteria for 'probable AD' [24], and MCI was defined by an operationalization of the criteria of Petersen et al. [9]. Based on a comprehensive neuropsychological test program, episodic memory was the only cognitive domain with significant impairment in this group. This cognitive profile was defined as an anterograde memory domain score below –2 SD on age-corrected norms, and other cognitive domain scores higher than –2 SD. Further, all MCI patients had normal basic functions on activities of daily living and a score on the CDR of 0.5. Patients with a known or suspected cause for memory impairment, e.g. alcohol abuse, depression or anxiety disorder, were not classified as having MCI in order to include only amnesic MCI patients (as described by Petersen et al. [9]). Importantly, cognitive complaints from the patient or relative were not mandatory to meet the MCI criteria of this study.

The control group consisted of healthy elderly volunteers recruited by newspaper advertisement. 33 were selected from a cohort of 50 persons to match the 2 patient groups on age, education and premorbid intelligence. Healthy volunteers were excluded if they had a history of neurological or psychiatric disease, abuse of alcohol or drugs (including use of sedatives), head trauma, a family history of mental illness in first-degree relatives or an abnormal performance on the basic assessment. The basic assessment included a physical and neurological examination (including cognitive screening), a screening for psychiatric symptoms with the Brief Psychiatric Rating Scale [25] and a neuropsychological examination. Both patients and controls gave informed consent to participate in the study.

Cognitive Testing

Two methods for assessment of impaired awareness were used in both patient groups, and a Memory Questionnaire was applied in the control group.

Anosognosia Rating Scale

An experienced neuropsychologist (J.S.) rated the patient's level of awareness without knowledge of the results from the other awareness assessments. The categorical four-point scale from Reed et al. [19] was used with extensions. High inter-rater reliability has been demonstrated for the scale [19]. The level of awareness was divided into the following categories: 'full awareness', 'shallow awareness', 'no awareness', and 'denies impairment'. A detailed description of these categories can be found in the original paper. In this project two additional categories were added, since patients without memory impairment were included. The category 'not relevant' was used if no cognitive abnormalities were found and if the patient did not have cognitive complaints. The category 'subjective complaints' was used for patients with cognitive complaints but normal performance on all assessments of cognitive functions.

Memory Questionnaire

Patients and controls were given a self-rating questionnaire described by Michon et al. [21], originally adapted from Squire and Zouzounis [26]. The questionnaire consists of 20 items regarding their memory abilities, and parallel versions are filled out by both the patient and their relatives (questions can be found in Michon et al. [21]). Raters are asked to evaluate the current memory abilities of the patients as compared to 5 years ago. Ratings are made on a nine-point scale ranging from –4 through 0 to +4, giving a possible total

score from –80 to +80. If necessary, the patient was guided according to the method described [21]. The scores for the patient's own rating, the relative's rating and the difference between these (relative rating – patient rating) were analyzed.

Neuropsychological Battery

Neuropsychological testing of patients including the assessment of awareness was performed on two sessions on different days. Control subjects were examined in one session with the same tests. In the first session the Danish Mental Status Test (DMST) was applied. This test battery consists of 28 subtests, the majority being modifications of internationally well-known cognitive tests. These tests are grouped into six composite cognitive domains: memory, attention, abstraction, language, visual perception, and visuo-construction [27]. Based on the control material from Waldemar et al. [27] a computerized method for calculating composite domains corrected for age and education was developed. This method was used to evaluate performances in the six domains. For each domain a z score of –2.0 or lower was considered to indicate impairment. The patients' cognitive profile was classified according to this procedure. The level of the premorbid intelligence was assessed using Danish Adult Reading Test (DART), a Danish version of the National Adult Reading Test [28]. The Boston Naming Test was applied in the majority of patients.

At the second visit additional testing included Category Cued Recall (CCR) [29], Wisconsin Card Sorting Test, Stroop Test, Trail Making Test, Similarities (WAIS) and Design Fluency. The second session was conducted by a different neuropsychologist than the one from the first visit, and the second examiner was unaware of the results from the first test session. The results from the first session were the primary source for the cognitive profile, but if impairments not previously described were found at the second session, these results could influence the diagnostic classification.

Statistical Analysis

Differences between the 3 groups concerning demographic variables and memory ability were performed using one-way analysis of variance (ANOVA) with pre-testing of homogeneity of variances and post hoc tests with Bonferroni corrected t tests. In comparisons of test results for the Memory Questionnaire the Kruskal-Wallis test was used due to inhomogeneity in the variances. Comparisons on a group-by-group basis were performed with Bonferroni corrected t tests for the Memory Questionnaire. The correlation between MMSE and the Memory Questionnaire results was analyzed using Spearman's rho and further assessed using linear regression with plots of residuals as model control. For the anosognosia rating scale differences in the proportion of patients with MCI and AD were examined using the χ^2 test, and Fischer's exact test (two-sided) was applied when cells had expected counts less than 5.

Results

Background Data and Memory Ability

The demographic data and the MMSE and CDR scores are presented in table 1 for control subjects and for patients with MCI and AD. No significant effect of group was found for age ($F(2,96) = 2.56$, $p = 0.082$) or education ($F(2,96) = 0.68$, $p = 0.51$). A significant effect of group was found for premorbid intelligence measured by DART ($F(2,94) = 3.09$, $p = 0.050$), but no significant differences were found using Bonferroni corrected t tests. The memory performances in all groups as measured by the CCR are also displayed in table 1. We found a significant effect of group for both immediate ($F(2,94) = 53.3$, $p < 0.001$) and delayed recall ($F(2,91) = 61.3$, $p < 0.001$). Using Bonferroni corrected t tests we found no significant difference between patients with MCI and AD for immediate ($p = 0.53$) or delayed recall ($p = 0.59$).

Table 1. Demographic data and results from MMSE, CDR and CCR

	Controls (n = 33)	MCI (n = 30)	Mild AD (n = 36)
Females/males	19/14	16/14	21/15
Age, years	73.4 ± 5.3 (64–84)	74.4 ± 4.8 (66–84)	76.4 ± 6.3 (62–87)
Education, years	11.7 ± 2.9	11.1 ± 2.9	10.9 ± 2.8
DART	33.6 ± 9.24	31.8 ± 10.7	27.3 ± 12.1
MMSE	29.3 ± 0.85 (27–30)	26.07 ± 2.06* (22–29)	24.04 ± 2.5*# (20–30)
CDR, n:score	33:0	30:0.5	21:0.5 13:1.0 1:2.0 1:3.0
Immediate recall CCR	35.3 ± 6.3	19.8 ± 8.0*	17.2 ± 8.6*
Delayed recall CCR	33.7 ± 7.8	16.6 ± 7.2*	14.0 ± 8.0*

Unless otherwise indicated the values are means ± SD (ranges).
* Significant difference from controls: $p < 0.05$.
# Significant difference from MCI: $p < 0.05$.

Memory Questionnaire

The results from the Memory Questionnaire are presented in table 2. Significant effects of groups were found for all three measures of the Memory Questionnaire, own report (χ^2 (2) = 13.05, $p = 0.001$), relatives report (χ^2 (2) = 42.73, $p < 0.001$), and the difference between these (χ^2 (2) = 17.32, $p < 0.001$). On the self-report part of the Memory Questionnaire a significant difference was found between mild AD and controls ($p = 0.006$), but not between MCI and controls. For relatives' report and the difference between patient and relative rating, significant differences were found between controls and both patient groups. Thus, there was no significant difference in subjective memory complaints in MCI versus controls.

The impact of MMSE on the impairment of awareness was assessed for pooled groups of patients with MCI and

Table 2. Results from the Memory Questionnaire (means ± SD)

	Memory Questionnaire		
	patient's report	relative's report	relative's report – patient's report
Controls (n = 33)	–7.94 ± 10.8	–5.17 ± 9.4	3.42 ± 12.1
MCI (n = 29)	–17.5 ± 20.6	–30.8 ± 19.6*	–12.44 ± 20.6*
Mild AD (n = 36)	–20.69 ± 17.6*	–40.73 ± 16.5*	–20.58 ± 25.2*

Data are missing for all measures for 1 of the 30 MCI patients.
* Significant difference from controls: $p < 0.05$.

AD. For the Memory Questionnaire no significant correlation between MMSE and patient report was found (r = –1.26, p = 0.32). MMSE was identified as a dependent factor for both relatives' report ($r^2 = 0.071$, $F(1,58) = 4.46$, $p = 0.039$) and the difference score ($r^2 = 0.145$, $F(1,58) = 9.83$, $p = 0.003$), with the largest proportion of the variance explained in the relation between MMSE and difference score. Thus MMSE correlated significantly to relatives' report but not to the patients' own report.

Anosognosia Rating Scale

The classification within each of the patient groups on the Anosognosia Rating Scale is presented in figure 1. The scores 'not relevant' and 'subjective complaints' were not applied in these patient groups, since all patients had amnesia. The results showed no differences between MCI and AD patients classified in the categories 'full' ($\chi^2 = 0.019$, $p = 0.89$), 'shallow' ($\chi^2 = 0.563$, $p = 0.45$) and 'no awareness' ($p = 0.33$). In total 8 mild AD and 3 MCI patients had 'no awareness' of deficits and less than half of all patients had 'full awareness'.

The correspondence of the Anosognosia Rating Scale and the Memory Questionnaire was assessed by analyzing the scores from the Memory Questionnaire classified by ratings on the Anosognosia Rating Scale. Results are presented in table 3. A significant effect of group was found when examining scores for the self-report part of the Memory Questionnaire. Post hoc t tests with Bonferroni correction showed significant differences in the scores on the Memory Questionnaire for all 3 groups. For the difference measures of the Memory Questionnaire significant group effects were also found ($F(2,51) = 15.5$, $p < 0.001$), and the 3 groups differed significantly with post hoc t tests with Bonferroni correction. No significant group effect was found for relatives rating ($F(2,51) = 1.44$, $p = 0.25$). Thus, Memory Questionnaire scores corresponded well with the classification by clinician.

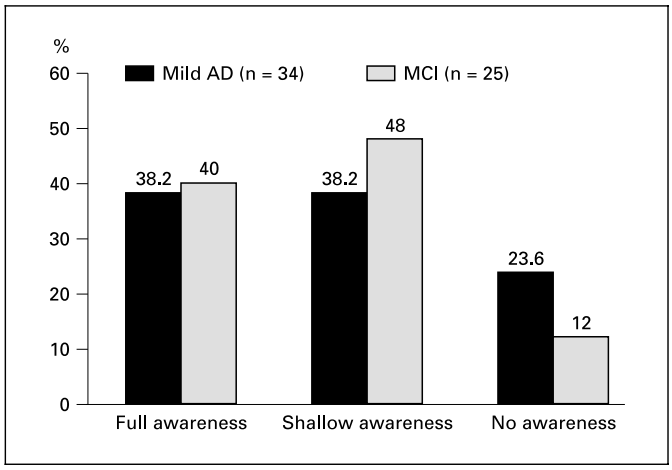

Fig. 1. Classification of patients on the Anosognosia Rating Scale. Note: Of the 66 patients included in the study, data on the Anosognosia Rating Scale are missing for 2 AD patients and 5 MCI patients.

Discussion

In this study impairment in awareness was assessed by clinician's evaluation and memory questionnaires in patients with mild AD and amnesic MCI. For both methods of assessment we found impaired insight for memory deficits in mild AD and MCI. The results showed large individual differences in the degree of impairment ranging from normal (full) insight to severe loss of insight in both patient groups. Previous studies have demonstrated that limited insight in symptoms and their implications are common in the early stages in AD [2, 4, 30]. Amnesia has been the predominant area of interest [21], but anosognosia in AD has also been found for behavioral changes [31], functional deficits [32], social interaction and emotional control [33].

As explicitly assessed by questionnaires and clinician's evaluation, the level of awareness concerning memory

Table 3. Results from the Memory Questionnaire from 58 AD and MCI patients as classified by the Anosognosia Rating Scale (mean ± SD)

Anosognosia rating	Memory Questionnaire		
	patients' rating	relative's rating	difference
Full awareness (n = 23)	−32.91 ± 22.17*	−30.52 ± 20.78	2.05 ± 17.87*
Shallow awareness (n = 24)	−14.38 ± 8.58#	−39.35 ± 16.33	−24.65 ± 17.01#
No awareness (n = 11)	−7.00 ± 14.55	−39.40 ± 18.97	−31.80 ± 24.51

Of the 66 patients 7 had no anosognosia rating, and all measures of the Memory Questionnaire are missing for 1 patient.

* Significant difference from no and shallow awareness: $p < 0.05$.

Significant difference from no awareness: $p < 0.05$.

functioning was not significantly different in mild AD versus MCI, indicating that limited insight is equally frequent in amnesic MCI and in mild AD. If the degree of amnesia in mild AD patients had been more severe than in MCI patients, this could imply that the level of insight was actually relatively lower in the AD group. However, no significant differences between the groups were identified, and the comparable levels of amnesia strengthen the hypothesis that MCI and mild AD patients demonstrate the same level of impaired awareness. Based on these results we assume that impaired awareness concerning memory deficits is common not only in early AD, but that it is present on the group level to the same degree in MCI. In our data group differences on cued recall between the 2 groups were not apparent, but cued episodic learning has previously been found to decrease with dementia severity [34]. We restricted our analysis in AD patients to very mild dementia and hypothesize that a relationship could be found in more severe stages.

Few studies have been published on awareness of memory dysfunction in MCI. From these it seems unclear whether subjective complaints are characteristic in MCI, as indicated in the commonly used criteria of Petersen et al. [9, 10], although these suggest that memory complaints should preferably be corroborated by an informant. Two studies found that elderly persons with memory impairment identified on cognitive testing do not have diminished insight into their amnesic difficulties [15, 17], whereas others have indicated that MCI patients display poor insight concerning memory dysfunction [14, 16, 35] and functional abilities [13]. Recently, studies have demonstrated that impaired awareness of olfactory and functional deficits in MCI patients may be a diagnostic marker for AD [11, 12]. From these previous studies it is difficult to draw conclusions on awareness in MCI, since different methodological approaches have been applied. Awareness was not the predominant area of interest in some of these publications, and assessment of insight has not always been thorough. Further, different MCI criteria have been applied. In some instances broad definitions probably led to inclusion of different types of memory-impaired patients (subtypes have been proposed by Petersen et al. [9]). Based on the majority of previous reports and on our results, it seems reasonable to assume that some MCI patients may be more impaired than they subjectively report. This may be a problem in population-based studies if subjective complaints are part of the inclusion criteria. In a recent study it was found that only half of future dementia cases reported memory problems before diagnosis [36]. In clinical settings reports from informants combined with a thorough clinical interview and observation are central, and subjective memory problems should not be a mandatory prerequisite when assessing suspected dementia disorders.

One possible explanation for the poor insight in both MCI and AD is gradual adaptation due to the slowly progressing deterioration, but this does not explain the great variability in insight. The variability may be caused by lesions in different regions of the brain, some more important than others. Anosognosia in AD has been attributed to dysfunction in the frontal lobes [19] and in the right hemisphere [37, 38]. In the earliest stages of AD the medial temporal lobes are commonly affected [39], and amnesic patients with temporal lobe lesions have been demonstrated to have poor insight, although not as severe as patients with focal frontal or diencephalic lesions [40]. In disorders with selective amnesia, e.g. Korsakoff syndrome, patients exhibit impaired meta-memory [41], which has been linked to frontal lobe pathology [42]. Although neuropathological changes in the frontal lobes are not frequent in the earliest phases of AD, frontal lobe dysfunction may occur in some patients given the heterogenous nature of AD. Thus, frontal degeneration may be an explanation of poor insight in some patients. Psycho-

logical factors and the neuroanatomical basis for impaired awareness in MCI should be further investigated.

Anosognosia is not a unitary construct [43] and has been assessed with a range of methods, each having limitations [18]. Evaluations by clinicians are most widely used, but may be too global and might fail to describe the complexity of individual patterns of insight. Relatives' ratings have been used in many studies, but they rely on the assumption that carers are reliable informants, which can be questioned, although some validity for carer rating has been documented [30, 44]. Raters may be influenced by a number of factors such as caregiver burden [8] and the frequency of time spent with the patient might be highly variable. For evaluation in individual cases, difference scores are rarely used. Assessments based on discrepancies between expected performances as predicted by the patient and actual performance on cognitive tests could be relevant, but are somewhat unfeasible in daily practice, because questionnaire measures and neuropsychological testing should be comparable and because the tasks should be familiar, everyday tests [18]. In daily clinical practice where short and reliable testing is required, a short evaluation by the clinician is most feasible, but other methods may be applied for specific purposes.

Awareness ratings for the memory-impaired patients on the Anosognosia Scale were classified into 3 groups. When analyzing the results from the difference score on the Memory Questionnaire by awareness level, significant differences between all groups were found. This demonstrates that an experienced clinician can assess the level of awareness as demonstrated by discrepancy scores, which is a confirmation of the short, global assessment. This good correspondence between the two methods indicates that parallel versions of questionnaires will not lead to additional information. However, multiple methods of assessment may be relevant for more complex descriptions of awareness. In particular, multi-modal assessment of awareness is very relevant in research on awareness, since some of the above-mentioned methodological difficulties might be avoided.

The difference between patients' and relatives' report on the Memory Questionnaire was found to be significantly dependent on the MMSE, with awareness decreasing with lower MMSE scores. Thus, although no group differences were identified between MCI and mild AD patients in the level of awareness, the severity of cognitive impairment might be a dependent factor for poor insight in memory impairment when assessed cross-sectionally. MMSE and awareness have been found to be correlated in AD [4], but the relationship may not be apparent, unless controlled for depressive symptomatology [45]. Sevush [46] described that anosognosia correlates slightly with dementia severity in cross-sectional studies, and is independent of disease progression when assessed longitudinally. Based on our results and previous reports we hypothesize that impaired awareness is most frequent in severe AD, but that large individual differences exist, and that insight may be severely impaired in the earliest stages of AD – even in MCI.

To summarize, using multi-modal assessment of awareness we identified that impaired insight was equally frequent in amnesic MCI and in mild AD, and that significant individual heterogeneity was found in the degree of impaired insight in both groups. Our results imply that lack of subjective complaints does not exclude the presence of a cognitive disorder. Information from MCI and AD patients concerning their cognitive status should be questioned and an attempt to obtain an account of the cognitive impairment from an informant should be made. This may be a particular problem in MCI patients who, more frequently than AD patients, come on his/her own to a memory clinic.

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