Transition from Cognitively Impaired Not Demented to Alzheimer's Disease: An Analysis of Changes in Functional Abilities in a Dementia Clinic Cohort

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Key Words

Mild cognitive impairment • Disability Assessment of Dementia • Alzheimer's disease • Functional abilities • Cognitively impaired not demented • Functional Rating Scale

Abstract

Background: Patients with cognitive impairment no dementia (CIND) are at an increased risk of progression to Alzheimer's disease (AD). Whether subtle impairments in functional or social abilities at the CIND stage can predict progression to AD is not yet fully determined. We evaluated whether impairments on the Disability Assessment for Dementia (DAD) and Functional Rating Scale (FRS) can predict progression to AD. **Methods:** We examined 70 patients with CIND from the ACCORD cohort having complete DAD and FRS baseline and 2-year follow-up data. MANCOVA adjusted for age, sex, education and baseline MMSE score compared the baseline and 2-year change in DAD and FRS scores in CIND patients who progressed to AD versus non-progressors.

Results: There were no significant differences between CIND progressors and non-progressors in baseline total DAD or FRS scores. FRS domain analysis revealed that greater impairment in social/occupational functioning significantly predicted progression, while there were no predictive DAD domains. In progressors, both DAD and FRS scores significantly declined over time with the largest changes in instrumental activities of daily living (IADL). **Conclusion:** While changes in IADL characterize the progression from CIND to AD, impairment in complex social-cognitive competency significantly predicts risk of progression and may mark early AD.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in older adults affecting 5–10% of individuals over the age of 65 in North America [1]. Even more individuals are afflicted with milder degrees of cognitive dys-

function such as mild cognitive impairment (MCI) [2]. Although the state of MCI often represents a transition state between normal and probable AD in many individuals [3], the defining features of this state are still evolving [2]. The most widely used operational criteria for MCI at the present time specify that functional abilities are generally normal [4].

Cognitively impaired not demented (CIND) is a classification term that has been used in population-based epidemiological studies to capture a broad range of these milder forms of impairment in cognition [5, 6]. By definition CIND permits the inclusion of all individuals who fall below normal but do not meet dementia criteria within a diagnostic category [5, 6]. CIND does not require any specific domain(s) of cognitive impairment [5, 6]. It can be applied in clinical settings for referred patients seeking assessment of their cognitive difficulties. However, the breadth of this categorization is also accompanied by significant heterogeneity in its clinical, behavioural and neuropsychological features [7, 8]. CIND can be subclassified aetiologically into groups of suspected pre-AD, vascular cognitive impairment/no dementia, associated with psychiatric diagnosis, associated with other medical and neurological conditions, and those with no obvious aetiology (not otherwise specified, NOS).

In the Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD), 34% of CIND patients progressed to dementia after 2 years, while 53% remained CIND and 14% improved to be diagnostically categorized as not cognitively impaired (NCI) [9]. An examination of the relationship between aetiology and outcome has shown that those with pre-AD and vascular cognitive impairment/no dementia have the highest rate of progression (40% over 2 years), while those with psychiatric CIND and CIND NOS are least likely to progress (24% over 2 years).

The prediction of outcome in both CIND and MCI has been studied extensively. Neuropsychological testing (NPT) has been used to define those tests or patterns of impairment that predict progression to AD [8]. However, NPT is often a limited resource in clinical settings, and the accuracy of NPT predictors has not always been consistently high [10]. As the current diagnostic criteria for dementia require that cognitive problems impair daily functioning, a detailed assessment of functional abilities is a logical alternative to NPT as a tool to predict and identify the early stage of dementia and AD [11]. It is likely that subtle to mild functional impairments are present some time before the criteria for dementia and AD are met. Non-demented elderly subjects with limitations in

activities of daily living (ADL) have been found to be at an increased risk for progressing to dementia during a 3- to 5-year follow-up [11, 12]. In particular, limitations in instrumental activities of daily living (IADL) have been a strong predictor of progression to dementia, with the risk increasing as a function of the number of impaired IADL [12]. Beyond ADL, recent studies have demonstrated that impairment in complex everyday competencies requiring high-level social and cognitive functioning is more prevalent in subjects with MCI compared to healthy controls [13–15]. We hypothesized that the identification and characterization of early impairments in IADL and complex social-cognitive competencies would be predictive of progression of CIND.

In the current study, we analysed subjects with CIND who participated in a 2-year longitudinal study and had prospectively undergone comprehensive assessments of everyday social and functional ability using the Disability Assessment for Dementia (DAD) [16] and the Functional Rating Scale (FRS) [17]. The main objectives of the current study were: (a) to characterize functional impairment in patients with CIND on the DAD and FRS; (b) to examine whether baseline functional impairment as measured by the DAD and FRS can discriminate or predict progression of CIND to AD, and (c) to identify longitudinal patterns of functional change as CIND patients progressed to AD.

Methods

The ACCORD is a prospective longitudinal cohort of patients referred to 8 dementia clinics across Canada. Details of the ACCORD study methods and baseline data have previously been published [7, 9]. Each site obtained informed consent and Institutional Review Board approval for the study protocol prior to initiating the study. Of the 1,136 patients in the cohort, 670 were diagnosed as having dementia by DSM-III-R criteria [18], and 342 were diagnosed as having CIND who met at least 1 criterion of the DSM-III-R but did not meet all the DSM-III-R criteria for dementia. People were diagnosed as NCI ($n = 124$) when they did not have any of the DSM-III-R criteria for dementia. Investigators completed the DSM checklist based on all available clinical, laboratory and neuro-imaging information.

All subjects participating in the current study subsequently underwent serial evaluations that included clinical and neuropsychological examinations, as well as the administration of the Mini-Mental State Examination (MMSE) [19], the FRS and the Cumulative Illness Rating Scale [20]. Additional informant-based assessments including the DAD and the Neuropsychiatric Inventory [21] were obtained from caregiver interviews.

The DAD is an informant-based scale with a total of 40 items: 23 items of IADL within the domains of meal preparation, telephoning, handling of finance and correspondence, planning/go-

Fig. 1. Study flow chart.

ing on an outing, taking medications, and participating in leisure and housekeeping activities, and 17 items of basic activities of daily living (BADL) in the domains of eating, continence, dressing and personal hygiene. The total score is presented as the percentage of all items that an individual can perform. For example, a score of 100% indicates that an individual can perform all 40 items independently whereas a score of 0% reveals that none of the 40 items can be undertaken. For items that are not applicable (e.g. for an individual who has never cooked in his/her life) there is a 'not applicable' option, and the total score is calculated with the item excluded from the denominator. Each of the 40 DAD items is also rated with respect to whether the impairment is a result of problems in initiation, planning/organization or performance.

The FRS is a clinician-rated multi-dimensional scale that is derived from the Clinical Dementia Rating Scale [17]. It consists of 8 domains including: memory, social and occupational functioning, home and hobbies, personal care, language, reasoning, affect and orientation. Its ratings are done taking into account the subject's history as well as collateral information and examination findings [17, 22]. Each domain is scored from 1 to 5, with 1 being normal and 5 being most severely impaired. Total FRS scores are calculated by adding up the individual domain scores with a range of 8 (normal) to 40 (most severely impaired). To facilitate comparison between the DAD and FRS in the current study, we transformed the raw FRS scores into percentages so that

100% represented normal function (i.e. 8/40 on the raw scale) and 0% denoted the most severely impaired score possible (i.e. 40/40 on the raw scale).

In this study, we examined patients who were diagnosed as having CIND at baseline and who had complete data on the DAD and FRS scales at both baseline and at the 2-year follow-up (fig. 1). We further classified the CIND subjects at the time of the 2-year follow-up into two subgroups: (1) CIND patients who did not progress (CIND-N) and (2) CIND patients who progressed to AD based on NINCDS-ADRDA criteria (CIND-P) [23]. We used a cohort of AD subjects who had the DAD at baseline and 2-year follow-up as a comparison group to our two CIND subgroups. Descriptive statistics were provided for the demographics of the two CIND subgroups and the AD group. The χ^2 test was used to compare proportions of categorical variables (i.e. sex and individual DAD items) between the two CIND groups, and the Student t test for two independent samples was performed to compare numerical variables (i.e. age, years of education, total MMSE, Cumulative Illness Rating Scale, and total and subscores on the DAD and FRS) between CIND-N and CIND-P. To account for potential confounders such as age, sex, level of education, baseline MMSE score and effect of multiple comparisons, we used a multiple analysis of covariance (MANCOVA) model to compare the CIND-N and CIND-P groups on the total DAD and FRS scores and all of their subscores, at baseline and at the 2-year follow-up. DAD and FRS change scores over the two study intervals were

Table 1. Characterization of the CIND-N and CIND-P groups, with AD as the reference group

a Demographics and baseline characteristics

	CIND-N	CIND-P	AD
Number	42	28	160
Age, years	62.4 ± 10.4	72.3 ± 7.4**	73.6 ± 7.6
Gender, % female	43.8	45.5	61.3
Education, years	12.2 ± 3.8	13.0 ± 3.1	11.3 ± 3.4
MMSE baseline	27.9 ± 1.7	26.5 ± 1.8*	21.1 ± 4.8
MMSE year 2	28.1 ± 1.7	23.3 ± 4.1**	17.8 ± 6.5
NPI baseline	11.0 ± 20.1	4.3 ± 6.3	9.8 ± 10.9
NPI year 2	7.4 ± 13.3	9.3 ± 11.0	14.4 ± 15.0
CIRS baseline	5.3 ± 3.9	5.2 ± 4.3	4.4 ± 2.8
CIRS year 2	6.1 ± 3.9	5.3 ± 4.6	4.9 ± 3.3

b Aetiological classification

Aetiological subgroups	CIND-N n	CIND-P n
Pre-AD CIND	6 (14.3)	10 (35.7)
Vascular CIND	8 (19.0)	8 (28.6)
Psychiatric CIND	8 (19.0)	3 (10.7)
Other early neurodegenerative diseases	0 (0.0)	1 (3.6)
Other neuromedical conditions	4 (9.6)	3 (10.7)
NOS	16 (38.1)	3 (10.7)

NPI = Neuropsychiatric Inventory; CIRS = Cumulative Illness Rating Scale. * $p < 0.05$, ** $p < 0.005$; the Student *t* test was used to compare groups. Higher CIRS and NPI scores indicate a greater burden of illness and neuropsychiatric symptoms. AD demographics and baseline characteristics are provided for reference only but were not included in statistical comparisons. Figures in parentheses indicate percentages.

also compared. The DAD scores from the two groups were further analysed by each functional domain and by each individual item. The cognitive domains of initiation, planning and performance within the DAD among CIND-N and CIND-P were compared separately by use of an ANCOVA model.

Results

Of the 146 CIND subjects who returned for a follow-up at year 2, 66 had incomplete DAD data ($n = 62$ at baseline and $n = 4$ at the 2-year follow-up) and were excluded. Of the 80 subjects who had complete DAD and FRS data at baseline and follow-up, 10 progressed to a dementia other than AD and were also excluded. The analyses presented in the current study are based on the remaining 70

CIND patients who met all study inclusion criteria of having both an entry and year 2 DAD and FRS. For descriptive comparisons we also include a cohort of subjects within the ACCORD who were diagnosed as having AD at baseline ($n = 160$) and who had complete entry DAD and FRS data. We also compared CIND subjects with a baseline DAD ($n = 70$) to those without ($n = 62$), but found no significant differences in age, sex, level of education or baseline MMSE between the two groups.

At the 2-year follow-up, 6 (9%) CIND patients had improved to NCI, and 36 (51%) remained stable. These 42 subjects formed the CIND-N group. There were 28 subjects (40%) who progressed to AD and formed the CIND-P group. The demographics and mean baseline scores of the CIND groups are shown in table 1a with inclusion of the AD reference group for comparison. CIND-P subjects were significantly older than CIND-N ones and had significantly lower MMSE scores at baseline and at the 2-year follow-up. Table 1b characterizes the two CIND groups by aetiological classification. CIND aetiologies were associated with outcome, with those classified as pre-AD representing the highest percentage within CIND-P, and CIND NOS the highest percentage within CIND-N.

Tables 2 and 3 show the baseline and 2-year change scores on the DAD and the FRS, respectively, for the CIND groups and the AD comparison group. At baseline, there were no significant differences in the total DAD scores between the CIND-N and the CIND-P groups. Comparisons of each of the functional ADL domain scores as well as the BADL and IADL subtotals in the DAD scale did not reveal any significant differences either. When items were grouped by initiation, planning/organization and performance (data not shown), there were again no significant differences. For each of the 40 individual DAD items, the proportion of individuals with impairment did not differ between CIND-P and CIND-N (data not shown). On the FRS total scores there were no significant differences at baseline between the CIND-P and CIND-N groups. However, on the FRS domain of social and occupational function, the CIND-P group had a significantly lower mean score than the CIND-N group [69.6% (SD = 17.2) vs. 79.8% (SD = 18.5), $p = 0.02$].

The 2-year change scores indicated a greater decline in the CIND-P group on both the DAD and FRS scales. There were significant differences in every category of the DAD change scores ($p = 0.004$). In particular, the total DAD score declined by 12.0% (SD = 19.2) in the CIND-P group compared to an improvement of 0.4% (SD = 8.9) in the CIND-N group. Also, the decline in each of the 10

Table 2. Baseline and 2-year comparison of DAD total and subdomain scores

	Baseline DAD, %		2-year change in DAD, %		AD subjects (n = 160)	
	CIND-N (n = 42)	CIND-P (n = 28)	CIND-N (n = 42)	CIND-P (n = 28)	baseline DAD, %	2-year change in DAD, %
<i>Total DAD score</i>	94.8 ± 10.8	94.1 ± 7.6	0.4 ± 8.9	-12.0 ± 19.2*	76.0 ± 20.0	-18.2 ± 22.0
Instrumental domains						
Meal preparation	92.6 ± 23.5	93.7 ± 22.7	-2.3 ± 19.8	-14.0 ± 40.5*	71.5 ± 37.4	-28.7 ± 46.5
Telephone	93.2 ± 19.8	90.0 ± 19.7	2.6 ± 21.4	-11.0 ± 25.5*	71.8 ± 33.4	-20.9 ± 37.6
Outing	93.2 ± 21.3	87.7 ± 21.8	3.9 ± 17.1	-14.2 ± 31.9*	59.9 ± 38.8	-23.1 ± 36.9
Finance and correspondence	89.8 ± 24.2	92.8 ± 14.4	-0.7 ± 27.1	-25.4 ± 36.2*	55.5 ± 35.9	-22.9 ± 37.5
Medications	94.4 ± 19.1	83.3 ± 30.9	-4.4 ± 25.7	-19.2 ± 38.4*	48.5 ± 47.3	-14.8 ± 48.2
Leisure and household	89.4 ± 23.7	87.0 ± 22.6	-1.1 ± 23.9	-14.0 ± 38.0*	73.1 ± 30.0	-20.3 ± 37.9
<i>Total IADL</i>	91.9 ± 17.5	89.8 ± 12.6	0.21 ± 12.8	-15.7 ± 22.8*	64.3 ± 27.0	-21.9 ± 26.2
Basic domains						
Hygiene	98.5 ± 7.4	100 ± 0.0	1.2 ± 7.7	-9.7 ± 22.2*	89.5 ± 23.1	-19.8 ± 36.2
Dressing	98.3 ± 5.6	98.2 ± 5.9	1.7 ± 5.6	-5.5 ± 22.4*	91.8 ± 17.7	-15.0 ± 30.0
Continence	97.9 ± 10.1	100 ± 0.0	-2.1 ± 23.0	-2.3 ± 10.7*	96.6 ± 13.9	-8.8 ± 26.0
Eating	98.6 ± 6.7	100 ± 0.0	-0.7 ± 10.8	-9.1 ± 23.4*	90.6 ± 19.5	-4.2 ± 27.7
<i>Total BADL</i>	98.4 ± 4.3	99.4 ± 1.8	0.6 ± 5.3	-7.5 ± 18.5*	91.2 ± 15.8	-14.3 ± 24.4

* $p < 0.05$ by MANCOVA comparison of CIND-P 2-year DAD change scores compared to CIND-N 2-year DAD change scores (adjusted for age, sex, education and baseline MMSE). Negative change denotes worsening from baseline. AD baseline and 2-year change scores are provided for reference only but were not included in statistical comparisons.

Table 3. Baseline and 2-year comparisons of FRS total and subitem scores

	Baseline FRS, %		2-year change in FRS, %		AD subjects (n = 160)	
	CIND-N (n = 42)	CIND-P (n = 28)	CIND-N (n = 42)	CIND-P (n = 28)	baseline FRS, %	2-year change in FRS, %
<i>Total FRS score</i>	82.7 ± 8.2	79.6 ± 8.7	1.0 ± 6.9	19.4 ± 16.0**	60.9 ± 23.0	26.0 ± 20.9
FRS items						
Memory	67.3 ± 12.9	63.9 ± 12.7	-0.6 ± 12.9	-20.5 ± 16.7**	45.5 ± 10.4	-2.9 ± 3.0
Social/occupation	79.8 ± 18.5	69.6 ± 17.2*	-0.6 ± 12.9	-23.2 ± 28.0**	53.0 ± 16.9	-3.7 ± 4.1
Home/hobby	88.1 ± 15.8	83.0 ± 13.7	4.2 ± 18.2	-33.0 ± 19.3**	55.6 ± 18.0	-4.0 ± 4.0
Personal care	97.0 ± 8.2	97.3 ± 7.9	-1.2 ± 9.5	-12.5 ± 21.0**	85.0 ± 18.1	-5.0 ± 0.7
Language	82.1 ± 15.9	83.0 ± 19.3	-0.6 ± 15.1	-12.5 ± 24.1**	67.5 ± 19.8	-3.3 ± 4.5
Reasoning	78.6 ± 17.6	85.7 ± 16.7	4.2 ± 12.2	-21.4 ± 30.2*	53.3 ± 16.3	-3.1 ± 4.9
Affect/behaviour	70.2 ± 25.4	75.0 ± 20.4	1.2 ± 20.6	-13.4 ± 23.1	66.3 ± 19.4	-1.2 ± 5.0
Orientation	91.1 ± 13.3	86.6 ± 15.9	1.8 ± 10.2	-18.8 ± 25.1**	60.8 ± 17.6	-3.0 ± 4.4

* $p < 0.05$, ** $p < 0.005$; MANCOVA comparison of baseline and 2-year change FRS scores between CIND-N and CIND-P (adjusted for age, sex, education, baseline MMSE and DAD scores). The FRS raw score ranges from 8 (normal) to 40 (severely impaired). The scores in this table were transformed into percent-

ages to facilitate comparisons with the DAD such that 100% represents normal, while 0% means severely impaired. Negative change denotes worsening from baseline. AD baseline and 2-year change scores are provided for reference only but were not included in statistical comparisons.

Fig. 2. Comparison of DAD item patterns between CIND-P and CIND-N subjects at 2 years, and AD subjects at baseline.

ADL domains as well as the BADL and IADL subtotals were significantly greater in CIND-P compared to CIND-N subjects. A comparison of the DAD initiation, planning/organization and performance scores indicated a significantly greater decline ($p < 0.05$) in each score for CIND-P compared to CIND-N, with the largest percentage decline in planning/organization (15.8%; $SD = 24.3$), followed by initiation (12.9%; $SD = 25.7$) and performance (9.6%; $SD = 16.4$). Similar to the DAD, the 2-year declines on the mean total FRS score were significantly greater for CIND-P than CIND-N [19.4% ($SD = 16.0$) vs. 1.0% ($SD = 6.9$)]. All FRS domains, except for affect/behaviour, also revealed greater declines in the CIND-P group.

In the CIND-P group, the pattern of functional loss closely follows the baseline pattern of functional loss observed in the AD group (fig. 2). The DAD item describing the ability to organize finances and pay bills included the highest proportion of individuals with impairment both in the CIND-P and AD groups.

Discussion

In this study we have compared measures of social and functional ability to evaluate their ability to predict progression to AD in a cohort of CIND patients referred to dementia clinics. The DAD instrument is a well-validated measure of functional disability in dementia that addresses not only the traditional elements of IADL and BADL, but also their related cognitive processes, cross-referencing items to being those of initiation, planning/organization or performance. The FRS provides a broader assessment of both cognitive and non-cognitive elements of everyday life including social/occupational functioning. Our hypothesis was that deficits in both IADL and complex social-cognitive competencies would distinguish those individuals who would progress to AD (CIND-P) within the CIND cohort.

Our results indicate that the only early significant predictor of progression to AD is a decline in the domain of

social and occupational functioning as captured on the FRS scale. No IADL domain or individual item on the DAD, or any of the cognitive probes of the FRS, differentiated CIND-P at this early stage. As the CIND-P individuals progressed to an AD diagnosis, broad-based functional decline became evident on both scales involving IADL, BADL and cognitive competencies. Most notably, the transition from CIND to AD was characterized on the DAD by declines in IADL, including handling of finances, taking of medications, communicating by telephone or letters, and planning/organizing household chores. This pattern, though less severe, matched the IADL deficits observed in the parallel cohort of AD patients.

By comparing a traditional ADL scale to a more global multi-dimensional rating scale that incorporates social and functional ability, we have demonstrated that the earliest changes in functional abilities in AD likely reside in social and occupational function. According to the descriptors for this FRS domain, these changes can be characterized as an awareness in the patient and/or informant that there is decreased performance in demanding employment or social settings [17]. This impairment appears to be among the first signs of impending AD that can be identified by patients and those around them. Its presence should serve to alert clinicians to a significantly increased risk of AD in patients with CIND. To capitalize on this finding, it will be important to further investigate social and occupational function in a more detailed way, to refine our understanding of those items or aspects that are most critical to AD risk prediction.

It is equally important to note that despite our extensive scrutiny of IADL domains and items on the DAD scale, we did not identify any IADL deficits that could reliably predict early AD. We speculate that the functional domains tracked by the DAD fall below the threshold of the type of impairment that arises prior to the onset of diagnosable AD. By contrast the DAD appears to be most useful in CIND as a tool for tracking longitudinal changes that can aid the clinician in appreciating the transition to AD.

Our findings add to the current literature on functional deficits that can be detected in CIND and MCI, emphasizing the more subtle nature of the difficulties that may present in complex everyday competencies [14, 15]. They stand in contrast to two large population-based studies that report an increased risk of developing dementia in subjects with IADL limitations [11, 24]. There may be differences in the study samples that partly account for this discrepancy. The ACCORD study enrolled patients referred to specialized dementia clinics, while the other two studies assessed subjects from random community sam-

pling. The referral process may have brought individuals to attention earlier in the CIND continuum potentially influencing the level of functional impairment that was captured. The smaller sample size in our study and the consequent lower power may also have impeded the detection of effects that reached statistical significance in the previous studies involving larger sample sizes.

Our findings must also be interpreted within the other potential study limitations. While both the DAD and the FRS utilize informant input, the validated administration of the DAD mandates that there be an informant, whereas the FRS can be done without an informant based only on the examiner's observations and assessments. A number of CIND patients presented to clinics without informants, especially for the baseline visits when their symptoms were minor, therefore the DAD could not be done and they were excluded from this study. This is a reality we often encounter in clinical situations as many patients with milder CIND do not feel they need an informant in their first assessment or do not consent to one being contacted as they wish to keep their concerns private. To examine this potential source of bias, we compared CIND subjects with and without a baseline DAD ($n = 70$ and $n = 62$, respectively) but found no significant differences in age, sex, education or baseline MMSE. In previous studies, we have evaluated potential differences between subjects who returned for follow-up and those who did not. We found that CIND subjects who returned for the 2-year visit had a higher baseline MMSE score but were otherwise comparable on age, sex and education to those that dropped out of the study [9, 25]. This adds to the impression that our study sample was comparatively milder with respect to their cognitive impairment along the CIND continuum. Therefore, if bias is present, we would expect our estimate to be conservative. One might also speculate that perhaps in a more advanced CIND sample, difficulties in complex IADL in the DAD such as handling of finances would indeed signify a greater risk of progression to AD (fig. 2).

A final caveat is that there is a risk of circularity with the use of functional ability in the prediction of progression to AD, while it is also part of the diagnostic criteria for AD. We speculate that it might require a more biologically based definition of AD to alleviate this conundrum [26].

In summary, this study demonstrates that while evaluation of activities of daily living is an important component in evaluating patients with progressive dementia, it is the assessment of complex social-cognitive competency and occupational functioning that may provide the earliest indication of AD.

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