Predicting the rate of cognitive decline in Alzheimer disease: data from the ICTUS study

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Abstract

Background: Different rates of cognitive progression have been observed among Alzheimer disease (AD) patients. The present study aimed at evaluating whether the rate of cognitive worsening in AD may be predicted by widely available and easy-to-assess factors.

Methods: Mild to moderate AD patients were recruited in the ICTUS study. Multinomial logistic regression analysis was performed to measure the association between several sociodemographic and clinical variables and 3 different rates of cognitive decline defined by modifications (after 1 year of follow-up) of the Mini Mental State Examination (MMSE) score: (1) "slow" progression, as indicated by a decrease in the MMSE score ≤1 point; (2) "intermediate" progression, decrease in the MMSE score between 2 and 5 points; and (3) "rapid" progression, decrease in the MMSE score ≥6 points.

Results: A total of 1005 patients were considered for the present analyses. Overall, most of the study participants (52%) exhibited a slow cognitive course. Higher ADAS-Cog scores at baseline were significantly associated with both "intermediate" and "rapid" decline. Conversely, increasing age was negatively associated with "rapid" cognitive worsening.

Conclusions:

A slow progression of cognitive decline is common among AD patients. The influence of age and baseline cognitive impairment should always be carefully considered when designing AD trials and defining study populations.

Introduction

Alzheimer's disease (AD) represents the most common cause of dementia (1) and is characterized by cognitive and functional impairment, and neuropsychiatric disturbances. AD has been traditionally considered as a slowly progressive condition, with survival of approximately 8-10 years, and estimated cognitive decline of approximately 3 points per year at the Mini Mental State Examination (MMSE) (2)(3). Nevertheless, longitudinal studies and clinical trials have increasingly documented important intra- and inter-individual variability, and different rates of progression have been described. Several factors may likely contribute to such reported clinical heterogeneity (4): 1) true differences in the neurodegenerative processes and, thus, in the clinical course of the disease; 2) methodological aspects, such as diverse study populations, outcome measures, and times of observation; 3) different comorbidities and concomitant medications; and 4) social factors, such as different patient assistance, economic status, and accessibility to health-care.

Predicting the course of cognitive decline may have important practical implications. First, it may help clinicians at more adequately addressing the questions and worries of newly diagnosed AD patients and their families concerning the duration of the disease and its trajectory over time. Moreover, it may reduce biases when conducting observational studies and clinical trials enrolling AD patients. In fact, their "natural" tendency to progress faster or slower should be considered when interpreting the study findings (e.g., the effectiveness of the investigated treatment or intervention)(5). Finally, it has been argued that properly modeling the course of AD may facilitate the validation of putative biomarkers, better correlating with the rates of progression rather than with the severity of the disease.

To date, considerable attention has been addressed to the clinical definition and characterization of the rapidly progressive variants of AD (3)(6)(7). This has led to the identification of several genetic (e.g., ApoE genotype), socio-demographic (e.g., age, sex, and education), and clinical factors (e.g., focal neurological signs, specific neuropsychiatric disturbances, and visuospatial deficits) potentially anticipating a quick worsening of cognitive

functioning (3)(8)(9). Nevertheless, the available evidence is still conflicting and far to be conclusive. Surprisingly, less interest has been given to the clinical AD variants characterized by a slow cognitive decline, despite being commonly seen in the routine clinical practice.

The present study is aimed at evaluating whether the rate of cognitive worsening in AD may be predicted by widely available and easy-to-assess factors. Therefore, we measured the association between several socio-demographic and clinical variables and 3 different progression rates defined by modifications (over one year of follow-up) of the MMSE score in the Impact of Cholinergic Treatment USe (ICTUS) study.

Methods

Study design and participants

The ICTUS study has been previously described elsewhere (10)(11). Briefly, the ICTUS study is a prospective multicenter cohort study aimed at evaluating the clinical course, treatment outcomes, and socioeconomic impact of AD in Europe. It involved 29 participating centers from 12 European countries, all members of the European Alzheimer Disease Consortium (EADC), a network of clinical and research institutions specialized in the diagnosis and treatment of AD.

The following inclusion criteria were adopted in the ICTUS study: 1) diagnosis of probable AD made according to National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (12); 2) MMSE score ranging from 10 to 26; 3) living in the community with a well-identified informal caregiver; 4) absence of known conditions reducing to less than 2 years the patient's life expectancy; 5) ability to sign an informed consent. The study was approved by the Ethics Committee of the Toulouse University Hospital (coordinating center) and at individual centers by local or national ethical committees. All the study participants signed informed consent.

After the baseline assessment (between February 2003 and July 2005), participants were followed up for 2 years with mid-term re-evaluations every 6 months. At baseline and at each follow-up visit, a comprehensive clinical and neuropsychological assessment was performed.

The present analyses were restricted to the first 12 months in order to improve the clinical meaningfulness of our findings. In fact, considering the nature of AD disease as well as the continuous modifications of its phenotype, it is more clinically relevant to explore short-term outcomes among affected patients than investigating the predictive capacities of parameters over very long term. This approach could consent a timely prediction of short-term clinical trajectories, allowing clinicians to promptly plan and implement appropriate interventions. In parallel, we decided to limit our analyses in order to reduce as much as possible the effects of

patients lost during the follow-up due to: 1) drop-outs (a frequent occurrence in this kind of study participants) (13), and 2) mortality.

Overall, a total of 1,375 patients were recruited in the ICTUS study. Three hundred seventy participants were excluded for the present analyses because they drop out before the 12-month assessment. These patients were found to be not significantly different to those we considered in our study sample in terms of socio-demographic characteristics. Conversely, they were shown to be more cognitively (MMSE score: p=0,04; Alzheimer's Disease Assessment Scale – Cognitive subscale [ADAS-Cog] score: p<0,001) and functionally (Activities of Daily Living [ADL] score: p<0,001; Instrumental ADL [IADL] score: p<0,001) impaired at baseline.

Cognitive function tests

Cognitive performance was assessed using the MMSE (2) and the ADAS-Cog (14).

The MMSE includes 30 items focused at measuring different cognitive aspects (orientation, registration, attention, recall, and language). The total score ranges from 0 to 30 with higher scores indicating better cognitive performance. This tool has been frequently adopted to categorize the rate of cognitive progression in AD patients (3)(15).

The ADAS-Cog represents the most widely adopted cognitive outcome measure in AD trials. It includes eleven items assessing different cognitive domains (memory, language, and praxis). The total ADAS-cog score ranges from 0 to 70, with higher scores indicating greater cognitive impairment.

Cognitive progression groups

For the present analyses, ICTUS participants were grouped according to the cognitive modification (in terms of MMSE variation) occurring between the baseline and 12-month follow-up assessments. In particular, participants were divided into three groups describing:

1) "Slow" decline (i.e., decrease of MMSE score ≤1 point per year (16));

2) “Intermediate” decline (i.e., decrease of MMSE score between 2 and 5 points per year (17)(18)(3)); and

3) “Rapid” decline (i.e., decrease of MMSE score ≥6 points per year (3)).

We adopted the MMSE to define these groups mainly because prediction models of decline have commonly used this variable as outcome measure, providing a reference of what can be considered as a clinically meaningful cognitive decline (19). Moreover, the widespread clinical use of the MMSE may facilitate the understanding and implementation of the results of this study.

Functional ability tests

Physical function was assessed adopting the ADL (20) and the IADL (21) scales.

The ADL scale is a carer-administered questionnaire ranking adequacy of performance in the 6 functions of bathing, dressing, toileting, transferring, continence, and feeding. Patients score 1 for independence in each of the 6 functions. Higher scores indicate greater functional independence.

The IADL scale is a carer-administered questionnaire assessing adequacy of performance in the 8 tasks of using the telephone, shopping, preparing meals, housekeeping, doing laundry, using public transportation or driving, using medications, and handling finances. Patients score 1 for independence in each of the 8 tasks. Higher scores indicate greater functional independence.

Neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed with the 12-items version of the Neuropsychiatric Inventory (NPI) (22). The NPI consists of a retrospective (up to 1 month) assessment of 12 neuropsychiatric symptoms commonly presents in dementia. Each symptom is rated, when present, in terms of severity (ranging from 1, “mild”, to 3, “severe”) and frequency (ranging from 1, “occasionally”, to 4, “very frequently”). The score of each item is then

calculated by multiplying severity x frequency, thus obtaining a score ranging between 0 and 12. The total NPI score is finally obtained by adding all the single items scores (thus, ranging from 0 to 144) with higher scores indicating greater psychopathology.

Other variables

Socio-demographic (age, gender, education, and income), clinical (family history of AD, and AD duration; body mass index (BMI); self-reported diagnosis of diabetes, hypertension, ischemic heart disease, stroke, and seizures; parkinsonism, and focal neurological signs), and therapeutic (anti-dementia medications) data were recorded at the baseline assessment. The severity of dementia was assessed by using the Clinical Dementia Rating (CDR) (23) scale. The Zarit Burden Interview (ZBI) (24) was adopted for evaluating caregiver's burden.

Statistical analysis

For the present analyses, participants were grouped according to their rate of cognitive decline between the baseline and 12-month follow-up visits, as measured by MMSE score modifications. One-way analysis of variance (ANOVA) and Chi-squared tests were used to describe the continuous and categorical characteristics of the study sample across the three categories of cognitive decline. Multinomial logistic regression analyses were performed for estimating odds ratios (OR) and 95% confidence intervals (CI) of different continuous (i.e., age, ADAS-Cog, IADL, NPI) and categorical (i.e., gender, history of ischemic heart disease, history of hypercholesterolemia) independent indicators across the rate of "intermediate" and "rapid" cognitive decline, with "slow" decline as the reference group, as measured by MMSE score modifications over one year of follow-up. The selection of the potential indicators in the statistical model was based upon their significant difference across the three groups of cognitive progression. Statistical significances in the multinomial logistic regression analyses were defined

as $P<0.05$. Statistical analyses were performed using SPSS statistical software version 18.0.0 (IBM Corp, New York).

Results

Descriptive characteristics of the study sample at the baseline assessment are shown in Table 1. A total of 1,005 patients (women 64.5%) were considered for the present analyses. The sample population had a mean age of 76.1 (standard deviation [SD] 7.7) years. MMSE and ADAS-Cog scores at baseline were 20.6 (SD 3.9) and 20.3 (SD 8.9) respectively, indicating a mild to moderate cognitive impairment. Conversely, only the 11% of the cohort exhibited a greater dementia severity (i.e., CDR score equal or higher than 2). More than 90% of patients were under cholinesterase inhibitors (ChEIs) treatment.

At the 12-month visit, 523 participants (52.0%) showed a "slow" decline of cognitive performance. Three hundred sixty-two subjects (36.0%) presented an "intermediate" decline, and 120 patients (12.0%) experienced a "rapid" cognitive worsening. The three groups were comparable for what concerns socio-demographic characteristics and comorbidities. Differences between groups were observed for CDR ($p<0.001$), ADAS-Cog ($p<0.001$), ADL ($p=0.09$), IADL ($p=0.08$), and NPI ($p=0.02$) scores at baseline. In particular, participants exhibiting a "rapid" decline were found to be cognitively and functionally more impaired at the baseline. Moreover, "rapid" decliners had higher basal NPI scores, indicating a greater frequency and severity of behavioral disturbances, and higher likelihood of receiving ChEI treatment ($p=0.08$).

Table 2 shows the results of a multinomial logistic regression analysis for "intermediate" and "rapid" decline having the group of participants showing a "slow" decline as reference group. Higher ADAS-Cog scores at baseline were significantly associated with both "intermediate" (OR: 1.04; 95%CI: 1.02-1.07) and "rapid" (OR: 1.07; 95%CI: 1.04-1.10) worsening after 12 months of follow-up. On the contrary, increasing age was negatively associated with "rapid" cognitive decline (OR: 0.96; 95%CI: 0.93-0.99). Finally, higher NPI scores were found to predict the "intermediate" rate of cognitive decline (OR: 1.01; 95%CI: 1.00-1.03). Interestingly, the same trends were obtained when different cut-offs were used for grouping ICTUS participants according to their rate of cognitive decline (i.e., "slow" decline:

decrease of MMSE score ≤2 point per year; “intermediate” decline: decrease of MMSE score between 3 and 5 points per year; and “rapid” decline: decrease of MMSE score ≥6 points per year).

When the predictors were standardized per their SD (data not shown), we found that the increase of 7.7 years of age and of 8.9 points of ADAS-Cog were associated with 28.0% and 82.0% increased risk of following a “rapid” decline. In other words, the ADAS-Cog seemed to be a stronger predictor than age for “rapid” cognitive worsening.

Discussion

In the present study, we explored whether common socio-demographic and clinical characteristics are able to predict the rate of cognitive decline in AD. Overall, most of the study participants exhibited a slow cognitive course of disease. More severe cognitive impairment at the baseline was found to predict a faster cognitive decline over the 12 months of observation. On the other hand, older age was found to be protective for such "rapid" pattern of cognitive decline.

Longitudinal studies are increasingly documenting slow rates of progression among AD populations (16)(17)(25). Moreover, it has already been shown that treatment with ChEIs significantly increases the probability of a slow rate of cognitive decline (15). In our study, despite having adopted very strict criteria (i.e., decrease in MMSE score ≤1 point per year), such a slow rate of worsening was found to represent the most common cognitive trajectory (being observed in more than 50% of ICTUS participants). The proportion of slow decliners was significantly higher than that observed in previous studies (4)(15)(16). The slowly progressive variants of AD (defined according to the present operationalization) are probably less commonly observed in the routine clinical practice compared to our study. This may sustain the hypothesis that patients participating in clinical trials and observational studies may be overall healthier (and, maybe, cognitively healthier) compared to the general population (16)(26), thus experiencing a more favorable clinical course. In other words, the external validity (i.e., generalizability)(27) of our findings should be confirmed in other studies.

Beside these preliminary considerations, the clinical characterization of slowly progressive AD appears of special interest. In fact, it could consent the clinical identification of factors potentially associated with a more favorable course of the disease. Moreover, it could allow more adequately conducting and interpreting randomized controlled trials enrolling AD patients. In fact, the tendency of a sizeable proportion of participants to progress slower may bias the initial sample size analysis and/or the interpretation of the study findings (5). For example,

including more slow decliners in the treatment arm of an AD trial may lead to an overestimation of the effect size of the studied intervention. Conversely, if they are mostly allocated in the control group, this could reduce the chance of detecting a therapeutic effect.

In the present study, older age was found to be associated with a decreased likelihood of experiencing a faster worsening of cognitive functioning over the 12 months of follow-up. This result is in line with available evidence related to the natural history of AD, mostly reporting an inverse association between age at dementia onset and rate of cognitive decline (28)(29). This relationship has been also corroborated by several neuroimaging and neuropathological findings. Magnetic resonance imaging studies have described faster rates of whole brain and temporal lobe atrophy among younger AD patients (30). Pathological studies have reported greater neuritic plaque burden and neurotransmitter deficits in early-onset compared with late-onset AD (31). Accordingly, positron emission tomography studies have reported greater amyloid load in patients with early-onset AD (32). Finally, it has been observed that older individuals mostly develop specific histopathological subtypes of AD (called "limbic-predominant AD") that are clinically characterized by longer survival and less steep decline of cognitive function (33). Based on these considerations, the influence of age on the rate of cognitive decline should be properly considered when defining the study populations in AD trials.

As well established in literature, initial cognitive impairment was found to predict an unfavorable course of the disease. In this regard, ADAS-Cog scores at the baseline have been repeatedly shown to represent an important covariate affecting the rate of AD progression (34). That is, the milder the baseline cognitive impairment in a population observed within a trial, the slower the disease progression, and *vice versa*. Interestingly, our data do not confirm previous evidence indicating education, neurological focal signs, parkinsonism, and history of cerebrovascular diseases as predictors of rapid cognitive progression (3)(8)(9).

Our study has several strengths. The analyses were performed in a large sample of AD patients, recruited at numerous dementia clinics across Europe. Moreover, taking into account

the non-linear AD progression over time (25), we also considered duration and severity of dementia (as measured by CDR score) as potential confounders. Nevertheless, some possible limitations of our analyses should be discussed because potentially influencing our findings. First, the limited duration of the follow-up does not enable to draw conclusions concerning the medium- and long-term history of the cognitive decline in AD. Although the ICTUS study is characterized by a 2-year follow-up, we decided to limit the observation period to the only first 12 months. Such choice is justified by the attempt to improve the clinical meaningfulness of our findings by drawing useful information for short-term outcomes (rather than for more uncertain medium- and long-term endpoints). In fact, it is important to provide to physicians key criteria with which they can quickly and easily evaluate the risk of the patient for short-term clinical worsening. Second, several factors potentially affecting the overall health status of participants (thus directly or indirectly influencing their cognitive function) were not taken into consideration in the present analyses. Therefore, we cannot exclude that third factors not considered in our study might have affected or differently explain our findings. A further potential limitation is represented by the adoption of a single measure (i.e., the MMSE score) to define the rate of cognitive decline. Despite of being widely adopted, the MMSE does not comprehensively and accurately reflect the global cognitive functioning (e.g., it does not assess executive abilities).

In conclusion, a slow progression of cognitive decline is common among AD patients. The clinical characterization of the slowly progressive AD variants may have important practical implications, both in clinic and research settings. In particular, age and cognitive function should always be carefully considered when designing trials on AD and defining study populations. Further studies are needed to confirm and extend the present findings.

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Table 1. Baseline characteristics of the cohort. Values are expressed as % or mean ± SD.

	Slow decline (n=523)	**Intermediate decline** (n=362)	**Rapid decline** (n=120)	**p**
Age (years)	76.6 ± 7.1	75.8 ± 8.2	75.1 ± 8.5	0.12
Gender (women)	62.1	67.7	65.0	0.24
Education time (years)	8.2 ± 4.8	7.7 ± 4.5	8.0 ± 4.4	0.40
Low income (<750€/month)	24.3	20.4	28.3	0.10
Family history of AD	32.5	30.1	26.7	0.42
Disease duration (years)	0.3 ± 0.7	0.4 ± 0.7	0.4 ± 0.7	0.28
BMI	25.3 ± 4.1	25.0 ± 4.0	25.2 ± 3.9	0.66
Depression	23.9	24.3	30.8	0.27
Diabetes	12.6	10.8	9.2	0.48
Falls	17.8	15.5	14.3	0.52
Hypercholesterolemia	29.3	24.3	24.2	0.21
Hypertension	40.0	36.5	32.5	0.25
Ischemic heart disease	15.1	14.4	10.8	0.48
Stroke	9.2	7.5	4.2	0.18
Seizures	1.0	1.1	1.7	0.79
Neurological focal signs	2.3	4.2	3.3	0.29
Parkinsonism	2.7	4.5	2.5	0.31
CDR				<0.001
0.5	45.8	46.7	7.5	
1	43.6	42.5	13.9	
≥2	30.0	51.7	18.3	
ADAS-Cog	18.5 ± 8.0	21.2 ± 9.3	24.9 ± 9.8	<0.001
ADL	5.5 ± 0.8	5.5 ± 0.8	5.4 ± 0.9	0.09
IADL	5.1 ± 2.2	4.8 ± 2.1	4.6 ± 2.1	0.08
NPI	10.9 ± 11.9	12.9 ± 13.6	14.0 ± 12.9	0.02
ZBI	20.0 ± 14.7	21.0 ± 14.4	21.6 ± 13.8	0.49
ChEIs	47.0	49.2	58.3	0.08

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive subscale; ADL: Activities of Daily Living; BMI: body max index; ChEIs: Cholinesterase Inhibitors; CDR: Clinical Dementia Rating; IADL: Instrumental Activities of Daily Living; NPI: Neuropsychiatric Inventory; ZBI: Zarit Burden Interview.

Slow decline: decrease of MMSE score ≤1 point per year; intermediate decline: decrease of MMSE score between 2 and 5 points per year; rapid decline: decrease of MMSE score ≥6 points per year.

Table 2. Multinomial regression analysis exploring predictors of "intermediate" and "rapid" cognitive decline (reference group: participants showing "slow" cognitive decline).

	Slow decline (n=523)	**Intermediate decline** (n=362)		**Rapid decline** (n=120)	
	Ref.	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**
Age (years)	1	0.98 (0.96-1.00)	0.08	0.96 (0.93-0.99)	0.01
Gender (females)	1	0.10 (0.61-1.64)	0.10	1.96 (0.77-4.97)	0.16
CDR score	1	0.97 (0.62-1.52)	0.89	1.34 (0.72-2.52)	0.36
ADAS-Cog	1	1.04 (1.02-1.07)	<0.001	1.07 (1.04-1.10)	<0.001
ADL	1	1.12 (0.88-1.43)	0.36	0.98 (0.70-1.37)	0.89
IADL	1	0.99 (0.89-1.10)	0.81	1.03 (0.87-1.21)	0.76
NPI	1	1.01 (1.00-1.03)	0.03	1.00 (0.98-1.03)	0.69
ChEIs (yes)	1	1.03 (0.73-1.45)	0.86	0.74 (0.44-1.25)	0.27

ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive subscale; ADL: Activities of Daily Living; ChEIs: Cholinesterase Inhibitors; CDR: Clinical Dementia Rating; CI: confidence interval; IADL: Instrumental Activities of Daily Living; NPI: Neuropsychiatric Inventory; OR: odds ratio.

Slow decline: decrease of MMSE score ≤1 point per year.

Intermediate decline: decrease of MMSE score between 2 and 5 points per year.

Rapid decline: decrease of MMSE score ≥6 points per year.