The Journal of Nutrition, Health & Aging©
Volume 12, Number 10, 2008

RAPID COGNITIVE DECLINE IN ALZHEIMER´S DISEASE. CONSENSUS PAPER

M.E. SOTO[1], S. ANDRIEU[2,3,4], C. ARBUS[5], M. CECCALDI[6], P. COURATIER[7], T. DANTOINE[8], J.-F. DARTIGUES[9,10], S. GILLETTE-GUYONETTE[1,2,4], F. NOURHASHEMI[1,2,4], P.-J. OUSSET[1,2,4], M. PONCET[6], F. PORTET[11], J. TOUCHON[11], B. VELLAS[1,2,4]

1. Department of Geriatric Medicine, Toulouse University Hospital, France; 2. Inserm, Unit 558, Toulouse, France; 3. Department of Epidemiology and Public Health, Toulouse University Hospital, France; 4. University Toulouse III, Toulouse, F-31073, France; 5. Department of Adult Psychiatry, Toulouse University Hospital, France; 6. Department of Neurology, Marseille University Hospital, France; 7. Department of Neurology, Limoges University Hospital, France; 8. Department of Geriatric Medicine, Limoges University Hospital, France; 9. Department of Epidemiology and Public Health, Bordeaux University Hospital, France; 10. Inserm, Unit 897, Bordeaux, France; 11. Department of Neurology, Montpellier University Hospital, France

Abstract: The rate of cognitive decline in Alzheimer's disease (AD) varies considerably between individuals, with some subjects showing substantial deterioration and others showing little or no change over the course of the disease. These wide variations support the relatively new concept of Rapid Cognitive Decline (RCD). Patients with an accelerated rate of cognitive decline have showed to present a worse evolution in terms of mortality, loss of autonomy and institutionalisation. The conclusions from RCD studies conducted in the past years remain very heterogeneous and sometimes contradictory. This is possibly due to methodological differences, mainly the different "a priori" definitions of RCD used to identify rapid decliners. Consequently of this, there is considerable variation in reported frequency of patients with RCD which may vary from 9.5% to 54%. The lack of both consensus definition and consensual clinical assessment tools is one of the major barriers for establishing an appropriated management of rapid decliners in clinical practice. Presently, management of rapid decliners in AD remains to be a challenge waiting to better know predictive factors of a RCD. To date no specific guidelines exist to follow-up or to treat patients with this condition. This consensus paper proposes the loss of 3 points or greater in Mini-Mental State Examination (MMSE) during six months as an empirical definition of rapid cognitive decline to be used in routine medical practice and to be relevant for clinical-decision making in patients with mild to moderately-severe AD.

Key words: Rapid cognitive decline, Alzheimer's disease, older adults.

Glossary: AD: Alzheimer's disease; RCD: Rapid cognitive decline; CGA: comprehensive geriatric assessment; RF: risk factors; MMSE: Mini-Mental State Examination; AchEIs: Acetylcholinesterase inhibitors; ADAS-cog: Alzheimer's disease Assessment Scale cognitive component; HR: Hazard ratio; ADL: Activity of daily living; MNA: Nutritional Assessment; EPS: extrapyramidal signs; DLB: Lewy Body dementia; CDR: Clinical Dementia Rating; CVRF: cardiovascular risk factors; ApoE ε4: Apolipoprotein E (4); BuChE: Butyrylcholinesterase; MRI: magnetic resonance imaging; rCBF: regional cerebral blood flow; SD: standard deviation; CSF: cerebrospinal fluid; WMH: white matter hyperintensity; Abeta1-42: amyloid beta 1-42; t-tau: total tau protein

Introduction

The rate of cognitive decline in Alzheimer's disease (AD) varies considerably between individuals (1). The assessment of the natural course of AD in non-treated patients has shown an average loss of 3 points per year on the Mini-Mental State Examination (MMSE) (2, 3). More recent cohorts, such as the REAL.FR cohort (4), in which all patients received a comprehensive assessment every 6 months and nearly 90% of patients were treated with acetylcholinesterase inhibitors (AchEIs), have shown a decrease of about 2 points in the first year and 2 1/2 the second year of follow-up. However, these data hide wide variations with some subjects showing substantial deterioration and others showing little or no change.

These wide variations support the relatively new concept of Rapid Cognitive Decline (RCD), which reveals a growing need in the medical community to further understand this rapid progression of cognitive decline in AD. As a result, RCD studies have increased over the past years. It is helpful to classify these studies according to their approaches: descriptive, prognostic, or as studies which consider the predictive factors of RCD. Besides these papers, only few articles have taken into account the therapeutic options available for treating patients with this condition.

The assessment of how rapidly the disease is progressing has important implications in clinical practice and care planning, since this rate of disease progression may be the most important factor in determining prognosis (5). In fact, research shows that patients with RCD have a worse prognosis in terms of mortality, and loss of autonomy (6, 7, 8).

Several studies applied the MMSE to assess aggressive disease course (7, 9, 10, 11), whereas others on the Alzheimer's disease Assessment Scale cognitive component (ADAS-cog) (15). The conclusions from these studies remain very heterogeneous and sometimes contradictory. This could possibly be due to methodological differences, mainly the different "a priori" definitions of RCD used to identify rapid

Received September 15, 2008
Accepted for publication September 26, 2008

decliners. In fact, because of the different measures and definitions used in studies to identify rapid decliners, there is considerable variation in reported frequency of patients with this condition (see tables 1 and 2). The prevalence of patients experiencing a RCD may vary from 9.5% when RCD is defined as the gain of 7 or greater ADAS-cog points in 6 months, to 54% when RCD is defined as the loss of 3 or more MMSE points in six months. Given the non-negligible proportion of AD patients presenting RCD and their poorer prognosis, there is an imperative need for a clinical assessment tool that could provide early detection. However, currently there is lack of a consensual definition of RCD in AD. Subsequently, no consensual assessment tools are proposed for use in routine clinical practice.

The aim of this consensus paper is to elaborate an empirical definition of RCD for mild to moderately-severe AD patients, based on the clinical experience and on the prediction of an adverse outcome in the disease evolution in those patients presenting an episode of RCD. A follow-up and management of patients with RCD will be also proposed. This consensus combined evidence derived from a review of the literature along with an expert opinion, who met in Marseille, France in March, 2008.

Methodology

We aimed to identify all English written studies reporting rapid progression in AD, irrespective of the study design and setting. Ovid Medline (1970 to July, 2008), and Embase (1980 to July, 2008) were search by the use of both the medical subject heading (MESH) terms and the text word: [rapid cognitive decline OR fast cognitive decline OR cognitive decline AND Alzheimer's disease], [rapid progression AND Alzheimer's disease], [fast progression OR fast decliners AND Alzheimer's disease], [rapid decliners AND Alzheimer's disease]. The reference lists of all identified papers were hand searched for relevant articles related to the topic. Besides, those studies in which rapid and slower decliners were clearly identified, articles which studied the rate of cognitive decline and its associated factors were also included. Sixty-one articles were selected for the purpose of this consensus.

The concept of rapid cognitive decline

Presently, the medical literature has widely recognised that AD progression is heterogeneous amongst patients. For instance, some patients may present a faster continuous cognitive decline between the onset of the disease and the end. Other patients may simply experience an episode of RCD during certain moments over the course of the disease. Still further, patients may present a slower more progressive evolution which, appears to be the most common type of progression today. Currently, there is an accepted concept of what a "rapid decliner" should be considered: a patient experiencing a significant deterioration on specified dementia assessment scales, with a greater than average or expected loss, within a short period of time (13). Throughout the literature, many terms are used to describe an aggressive course of the disease such as: 'rapid cognitive decline', 'fast cognitive decline', 'rapid progression', as well as 'rapid cognitive loss'. However, these studies differ in their assessment tools and time periods. Moreover, they differ in their objectives. The majority of RCD studies aim to assess the associated factors, while others will focus on the prognosis with different outcomes.

Several studies have based measurements of an aggressive disease course by using the MMSE. Doody et al (2001) used the time taken to reach a 5-point decrease in MMSE score, which was thought to be a clinically meaningful deterioration, to identify patients with rapid disease progression. In this study, patients were divided at baseline into slow (0- to 1.9-point decline per year), intermediate (2- to 4.9-point decline per year), or rapid progressors (≥ 5-point decline per year) using estimated preprogression rates based on their initial MMSE scores and the self-reported delay time between the first symptoms and the diagnosis (9). O´Hara et al (2000) identified fast decliners as those patients who declined 3 or more MMSE points per year. The authors chose this cut-off point in response to half of their population (53%) demonstrating a decline of 3 or less points per year (10). Dumont et al (2003, 2005) initially proposed a loss of 3 points or more in 6 months (14). Then, in a second paper, they changed to a loss of 4 points or more in 6 months (7), as this cut-off was twice as rapid as O'Hara's proposal. Atchinson et al (2000), divided into fast, intermediate, and slow decliners based on the monthly rate of change on the MMSE, at the points that left the most equal group sizes. Fast decliners had an average monthly MMSE decline of 0.58 points (11). Another efficacy measure that used to study the rate of progression in AD is the ADAS-cog (15). This tool is often used to assess cognition in clinical trials. Farlow et al (2001, 2005) and Wilkinson et al (2007) used a 4-point or greater decline on the ADAS-cog in 6 months to identify patients with a faster course of the disease in placebo-treated patients from clinical trials of rivastigmine in AD (16, 17) and memantine (18), respectively.

Table 1 includes studies that investigated an aggressive course of AD. In the table, the aim of each study, the assessment scales, and time periods are presented. However, these rapid rates of cognitive decline measurement tools have not been tested in order to investigate their prognosis value in worsening disease. The question remains; what is the impact of a loss of ≥3 or ≥4 MMSE points per year /six months? What is the impact of a gain of ≥ 4 points in the ADAS-cog scale in the evolution disease?

RCD: searching for a definition

Before organising appropriate treatment and preventive measures of the underlying causes of an aggressive course of AD, the priority should be the identification of patients with a RCD along with an appropriate tool. With the lack of consensus on the definition of RCD, the assessment and tool is extremely diverse. To support daily medical practice, a RCD tool needs to be easy to use, quick, affordable, valid and reliable.

Table 1
Measurement tools to identify a rapid cognitive progression in dementia

Cohort-Study	Description	MMSE (SD) at inclusion	Objective	Assessment Tools and Period of Time	% patients with RCD
Doody et al [9]	298 community-dwelling AD patients. Mean (SD) age 70 (8.3) years Average follow-up (SD) of 3 (1.7) years	20 (6.3)	To test a calculated rate of initial decline prior to the first physician visit for its ability to predict progression during subsequent follow-up	MMSE Rapid progressors (≥5p per year), intermediate progressors (2-4.9p per year), slow progressors (0-1.9p per year)	22
O´Hara et al [10]	1062 community-dwelling AD patients. Mean (SD) age 74 (8.2) years Average Follow-up (SD) of 14.8 (3.0) months	18.4 (6.1)	To investigate predictive factors of RCD	MMSE Rapid decliner: loss of 3 or more points per year	46.1
ELSA cohort Dumont et al [7]	312 community-dwelling AD patients. Mean (SD) age 75.4 (6.7) years Follow-up for 1 year	17.4 (5.2)	To investigate predictive factors of RCD	MMSE Rapid decliner: loss of 4 or more points in 6 months	25
REAL.FR cohort Dumont et al [14]	340 community-dwelling AD patients. Mean (SD) age 77.3 (6.9) years Cross-sectional data at inclusion	20.2 (4.2)	To investigate factors associated with RCD	MMSE Rapid decliner: loss of 3 or more points in six months	54
Atchinson et al [11]	211 community –dwelling AD patients. Mean (SD) age 71.6 (7.4) years 1 year of follow-up	21 (4.3)	To investigate if a neuropsychological profile function at the time of diagnosis is associated with a rapid decline	MMSE Rate of change calculated as MMSE2-MMSE1/12 months. Fast, medium and slow decliners divided at the rate of change point per month	39
Masse et al [74]	342 AD patients Mean (SD) age 70 (7.4) years Average follow-up (SD) of 34.8 (18.9) months	21.3 (5.1)	To investigate whether lipid lowering agents are associated with a slower cognitive decline.	MMSE Slow and fast decliners according to cut-off of 1.8 points (median annual rate of decline in the total population)	47.9
Buccione et al [42]	43 AD patients Mean (SD) age of 72.7 (6.6) years 2 years of follow-up	19.1 (3.3)	To investigate the predictive value of neuropsychological and behavioural variables on the cognitive and functional decline	MMSE Slow and fast decliners defined according to the MMSE differential score fell < or > the overall sample median (cut-off 2.56 points/2 y)	51.2
Marra et al [41]	45 AD patients Mean (SD) age 66.5 (5.9) years 3 years of follow-up	19.9 (5.4)	To find neuropsychological predictors of progression in AD	MMSE Rapid decliners defined on the basis of their rate of decay at the MMSE score (>25%per year)	40
Farlow et al [17]	Meta-Analyses of 679 AD patients 26 weeks of placebo treatment in 4 randomised controlled trials. Mean (SD) age of 73.4 (7.9)	_	To assess efficacy of rivastigmine in AD patients with rapid disease progression	ADAS-cog Rapid decliners: 4-point or greater decline in 6 months	36

AD: Alzheimer´s disease; MMSE: Mini-Mental State Examination; ADAS-cog: Alzheimer's Disease Assessment Scale cognitive component; SD: standard deviation

There are a limited amount of studies aiming to propose a definition for RCD in AD. In a first paper, Soto et al. (2005) proposed the following RCD definition for use in clinical practice: a 4-point or greater loss on the MMSE within 6 months and the loss of at least 1 point on the MMSE during the following 6 months (19). This definition was based on the literature review and results from longitudinal prospective studies. The cut-off point of ≥4 was based on literature data showing that an average group decline is usually in the range of 2 to approximately 4 points per year without AchEIs treatment (3, 20). In this paper, the progression profile of rapid decliners in ELSA cohort was analysed. Almost half of the patients (43%) who lost ≥4 MMSE point in 6 months continued to lose at least 1 MMSE point in the next 6 months of follow-up.

However, what cut-off points should be used needs to be determined in light of both clinical significance and statistical justification, and be validated by a follow-up study. In this line, two recent papers (21, 22) have studied the predictive value of the loss of MMSE score in terms of different clinical adverse outcomes. Carcaillon et al (2007) (21), investigated different thresholds of cognitive decline measured by the annual loss of points in the MMSE score before the time of AD diagnosis, which best predicted mortality, in order to define when a subject could be consider as a fast decliner. Analyses were performed in 245 incident cases of AD from the PAQUID cohort, an unselective community population. Cox proportional hazard models were used to study the relation between cognitive decline and mortality and were controlled for education level, age, sex and MMSE score severity at inclusion. The significant threshold of decline associated with a higher mortality rate was a loss of 3 points per year in the MMSE score (HR=1.7, 95% CI 1.2-2.5), thus they proposed a loss of 3 points or greater in MMSE per year as a definition to identify rapid decliners.

In a similar way, Soto et al (2008) (22), investigated if there was a MMSE threshold of decline during the first 6 months of follow-up that predicted a worse disease progression at 2 year follow up. This was done so to propose a feasible definition of RCD for routine clinical practice. Worse disease progression was defined as attainment of 1 of 4 clinical end-points: institutionalisation, death, increased physical dependence or worsening of behavioural and psychological symptoms. Data from 565 community-dwelling AD patients from REAL.FR cohort were assessed. Patients were classified as rapid and non-rapid decliners according to 2 MMSE decline thresholds tested: ≥ 3 points and ≥ 4 points for decline over the first 6 months of the study. Cox proportional hazard models were used and were controlled for the Activity of daily living (ADL) score, education level, age, sex and MMSE score severity at inclusion. Patients with moderate disease and a loss of ≥ 4 points showed a significant increased risk of mortality (HR=5.6, 95% CI 2.0-15.9) and institutionalisation (HR=3.8, 95% CI 1.8-8.1) at 2 year follow up. An interaction between the MMSE decline during the first six months of follow-up and the severity score of MMSE at inclusion was found in mortality and institutionalisation outcome variables. Both MMSE thresholds were associated with a higher risk of physical decline in all severity stages of the disease (HR=1.7, 95% CI 1.2-2.4 for ≥ 3 points and HR=1.6, 95% CI 1.2-2.3 for ≥ 4 points). They concluded that the loss of 4 points or greater in MMSE during the first 6 months of follow-up was a predictor of worse clinical course in AD. They proposed this cut-off to define the category of patients presenting a RCD.

In the same REAL.FR cohort, Helmer et al (2007) (12), aimed to determine the predictive value of the 6-month evolution of the ADAS-cog score in initially mild to moderate AD patients on the risk of death or severe dementia after 2-year follow-up. They showed that mild to moderate AD patients who declined at least 7 points at the ADAS-cog scale during an initial period of six months were at higher risk of severe

Table 2
Proposed definitions for Rapid Cognitive Decline based on cohort-studies

Cohort-Study	Description	MMSE (SD) at inclusion	Objective	Outcomes	Definition	% patients with RCD
PAQUID Carcaillon et al [21]	245 incident AD cases from general population Follow-up of 13 years	17.5 (5.5)	To confirm the concept of fast decliners at the time of AD diagnosis which best predicts mortality	Mortality	Loss of 3 or more MMSE points per year	33.9
REAL.FR Soto et al [22]	565 community-dwelling mild to moderate AD patients. Follow-up of 2 years	20.2 (4.2)	To test the MMSE threshold of decline during the first six months of follow-up which best predicts a worse disease progression at 2 year follow up	Mortality Institutionalisation Physical decline Worsening of BPSD	Loss of 4 or more MMSE points in 6 months	13.6
REAL.FR Helmer et al [12]	536 community-dwelling mild to moderate AD patients. Follow-up of 2 years	20.2 (4.2)	To test the ADAS-cog threshold of decline during the first six months of follow-up which best predicts a worse disease progression at 2 year follow up	Mortality Severe dementia	Gain of 7 or greater ADAS-cog points in s 6 month	9.5

MMSE: Mini-Mental State Examination; ADAS-cog: Alzheimer's disease Assessment Scale cognitive component; RCD: rapid cognitive decline; BPSD: behavioural and psychological symptoms of dementia

dementia or death after two years of evolution (after adjustment on the MMSE score and ADL-disability at baseline), (RR=2.3, 95% CI: 1.2 - 4.3, p=0.0102). On the basis of these results, they proposed that the proportion of fast decliners (7 points or more of the ADAS-cog) after 6 months of treatment would be a clinically relevant judgement criterion for future trials. Table 2 resumes the three articles aimed to propose a definition of RCD based on the disease prognostic, one in general population (PAQUID cohort) the other two, in an AD outpatient population (REAL cohort).

Consequences of a rapid cognitive decline

In a sample of 81 AD patients with a MMSE ≥ 15, followed up for a mean of 5.53 years, Kraemer et al (1994) suggested that the rate of disease progression might be more important than the severity of disease for predicting the clinical course (5). Likewise, Doody et al (2001) found that rapid decliners at inclusion would continue to decline more rapidly (reaching the threshold of 5-point loss in MMSE in 1.6 years) compared to slow initial decliners (threshold in 2.3 years) (9). Capitani et al (2004), investigated in 91 AD patients, the predictive value of the early progression rate of AD on the evolution of later stages. They found that the course of deterioration tended to stay constant over time (23).

The relationship between the rate of cognitive decline at the initial disease phase and the risk of reaching clinical milestones in subsequent years was examined by Holtzer et al (2003) in a 5-year prospective study. Their study included 236 AD outpatients with a mean age of 73 years. Cox analyses showed that a fast decline during the first year was related to an increased disability and to receiving a level of care equivalent to institutional care (8). Consistent with this finding, Dumont et al (2005) showed in the ELSA cohort that rapid decliners, identified at the first 6 months of follow-up, became more depended, measured by the ADL scale during the following 6 months than non-rapid decliners (7).

In a group of 354 older persons with AD, Hui et al (2003) (6) discovered that mortality in AD is strongly associated with rate of cognitive decline. Each of the patients underwent an annual clinical evaluation that included the administration of 17 cognitive function tests spanning a 4-year period. To determine mortality risk, patients were divided into quartiles based on rate of cognitive decline. Cox models showed that compared with those with the least decline, the risk of death was increased more than 3-fold in the subgroup with mild decline, more than 5-fold in those with moderately rapid decline, and more than 8-fold in those with the most rapid decline.

Then, RCD is usually associated with a worse disease evolution no matter the end-point chosen (death, mortality, loss of autonomy…)

Predicitve factors of rapid cognitive decline

Alzheimer's disease epidemiological studies have documented tremendous variability (24), not only in measured progression rates, but also in associated and predictive factors of a rapid progression of the disease. This reported heterogeneity likely reflects multiple phenomena, including 1) true differences in disease progression rates between patients, such as anatomopathological lesions; 2) differing properties, ie, floor and ceiling, of the measures selected; 3) differences in the end points selected to represent progression (cognitive decline, functional decline, nursing home placement, or death); 4) other methodological differences, such as the number of patients, duration of follow-up, and interval between visits; 5) differences in medical comorbidities; and 6) differences in patient care.

Many characteristics of AD patients are associated with a more rapid rate of cognitive decline. Here we summarise the studies, which analysed the predictive factors of RCD. In these studies patients were divided in subgroups according to their rate of cognitive decline being identified as rapid or non-rapid decliners. Additionally, studies with the aim of evaluating the rate of cognitive decline taking into account the presence of different risk factors will also be mentioned (see table 3).

Table 3
Summarize of predictors of rapid disease progression in AD in the literature

Socio-Demographics
Young age of onset (<65 years) [25] (<70 years) (26)
Higher education level (27, 28, 29)
Nursing home placement (32)
Clinical characteristics
Poor nutritional status (7, 34)
Extrapyramidal symptoms (35, 36, 37, 38)
Clinical criteria of Lewy Body dementia (40)
Cognitive and Neuropsychological features
Deficits in executive function and attention at time diagnosis (11, 41)
Altered freehand copy of geometrical figures (42)
Behavioural and Psychological factors
Aggressiveness (47)
Agitation/restlessness (28, 48)
Visual hallucinations (39, 42, 46, 47)
Sundowning (48)
Cardiovascular risk factors
Atrial fibrillation (52)
Hypertension (42)
Angina (52)
cerebrovascular events (51)
Smoking habits (53)
Genetics
BuChE wild type allele (58, 59)
APOE ε4 allele (54, 55)
Brain imaging
Cortical atrophy (60, 61)
Low regional blood flow (63)
Biological markers
Low plasma levels of Abeta40, Abeta42, and s-CRP

APOE ε4: Apolipoprotein E(4); BuChE: Butyrylcholinesterase; AD: Alzheimer´s disease; s-CRP: high-sensitivity C-reactive protein; Abeta: amyloid beta

Socio-Demographics factors

Age

O´Hara et al (2002) found that age during the clinic visit < 75 years old was predictor of RCD (10). In this study, patients were identified rapid decliners as those patients who declined 3 or more MMSE points per year. Additionally, several studies found that the age of onset of AD may influence the rate of cognitive decline later on. Those patients with an onset of AD before the age of 65 declined significantly faster than late-onset patients. Results revealed a trend of over 2 years on the modified MMSE ($p<0.001$) (25). In another comparison of 178 AD patients, those who were 70 or younger demonstrated a greater, more rapid decline along with more severe pathology than patients older than 70 (26).

Education level

Education may provide a "cognitive reserve" that must be depleted to a certain threshold before dementia becomes clinically manifest and may influence the rate of cognitive decline. At higher levels of education, AD patients may be more advanced when dementia symptoms manifest. Subsequently, these patients experience a greater clinical progression. In support of this hypothesis, Stern et al (1992) reported a correlation between the numbers of years of education and the evolution of AD pathology (27). For a given clinical severity, parieto-temporal blood-flow was reduced further in patients with higher levels of education, indicating more severe pathology. Other authors were in agreement of this, finding a higher education level as a risk factor for accelerated decline in AD (28, 29). Despite high education level accelerates cognitive decline, it delays it in incident elderly AD patients (30). In discordance with these findings, Guk-Hee Suh et al (2004) did not find duration of formal education as a significant predictor of cognitive decline (31).

Others factors appeared to influence the rate of progression of cognitive decline. In a recent paper, institutionalisation was associated with accelerated short-term cognitive decline in 432 community-dwelling older persons with AD (32). Higher levels of spirituality ($p < 0.05$) and private religious practices ($p < 0.005$) were associated with slower rate of cognitive decline (33).

Neither sex (7, 10) nor caregiver burden (7) have not appeared as risk factors of RCD. Economical or marital statuses have not been yet evaluated.

Clinical characteristics

Nutritional status

In the ELSA cohort, RCD was defined as a 4-point or greater loss on the MMSE in 6 months. Multivariate regression analysis from 312 community-dwelling AD patients showed that an optimal nutritional status, measured by the Mini Nutritional Assessment (MNA), might delay RCD (7). In fact, higher MNA score (indicating a lower risk of malnutrition) had a protective effect against rapid loss on the MMSE in 6 months (OR=0.86, 95% CI 0.75-0.99). Accordingly to this, in a sample of 160 very mild AD patients, it was found that lower MNA score, and thus a poorer nutritional status, was predictor of a faster cognitive progression at one year of follow-up (34).

Extrapyramidal signs

Several studies have shown that AD patients who presented extrapyramidal signs (EPS), such as tremor, rigidity, and bradykinesia suffered from subsequent faster cognitive decline (35, 36, 37, 38). However, in a recent paper, Capitani et al, aimed to verify if EPS were associated with a high speed of cognitive decline in dementia patients with amnesic onset. The analyses of 1082 patients found no significant association between EPS and a more accelerated cognitive decline (39).

Lewy Body dementia symptoms

Extrapyramidal, psychotic, and subcortical symptoms are common in patients with Lewy Body dementia (DLB) but can be present in AD. Kraybill et al (2005) confirmed that AD patients with symptoms of DLB pathology are more likely to have a faster progression of the disease compared to patients with AD or LB pathology alone. The rate of decline in AD patients with symptoms of DLB was significantly faster on the Mattis Dementia Rating Scale over 18 months ($p < 0.03$) and MMSE over 6 months ($p < 0.04$) compared with AD or LB patients (40).

Cognitive and Neuropsychological features

At the time of diagnosis, patient's cognitive status could also be a useful predictor of the course of the disease:

Atchinson et al (2004) divided into fast, intermediate, and slow decliners his AD population. Patients showing significantly impaired performance on measures in attention and executive function at baseline had a more rapid decline over 1 year on the MMSE than those who did not, despite equivalent MMSE scores at baseline for all groups (11). O´Hara et al found that patients at first visit presenting moderate to severe aphasia and a MMSE > 7 were risk factors, as well, for RCD (10). Marra et al (2000) found that mental control abilities and attention-demanding tasks were predictors of RCD (41). In this study rapid and slow decliners were defined on the basis of their rate of decay at the MMSE score. Buccione et al (2007) showed freehand copy of geometrical figures and word fluency as predictors of RCD (42).

Accordingly, other different studies have analysed impaired performances at baseline on neuropsychological measures, which may also influence on the rate of cognitive decline in AD patients (43, 44, 45).

Behavioural and Psychological factors

Psychotic symptoms were found to be predictors of RCD, in a sample of 43 AD patients followed over a 2-year period (42). In this study, slow and rapid decliners were defined on the basis of cognitive indexes of disease progression. Additionally, the

relation of psychotic symptoms to the rate of cognitive decline in AD was examined during a mean of 2.2 years in 478 AD patients. In controlled analyses visual hallucinations were associated with more rapid global cognitive decline. However, delusions and misperceptions were not significantly related to cognitive decline (46). The predictive value of visual hallucinations for accelerating the rate of cognitive decline was also corroborated by other papers (39, 47).

A predictive value for a faster rate of cognitive decline has also been assigned to various behavioural and psychological symptoms such as an aggressive behaviour (47), agitation (28), or sleep disturbances (47). Recently, disruptive behaviour (wandering, verbal outbursts, physical threats/violence, agitation/restlessness, and sundowning) was examined in order to study its ability to predict cognitive decline. The simple size included 497 patients with early-stage AD, followed for a mean of 4.4 years. The presence of at least 1 disruptive behaviour was associated with increased risk of cognitive decline (HR 1.45, CI 1.03-2.03). In particular, sundowning and agitation/restlessness were associated with a faster rate of cognitive decline (48).

Cardiovascular risk factors

While there is considerable epidemiologic evidence that cardiovascular risk factors (CVRF) increase risk of incident AD, few studies have examined their effect on progression after an established AD diagnosis. In a first paper, Barghava et al (2006) followed 247 mild AD patients for 3 years. Patients who progressed to the moderate stage (Clinical Dementia Rating (CDR) 2) were designated as fast progressors, and those who remained in the early stage (CDR 1) were designated as slow progressors. CVRF such as history of heart problems, stroke, hypertension, diabetes, or past or current smoking did not differ between groups (49). In accordance with these findings, Regan et al in 2006 found in an 18-month follow-up, that there was no significant difference in rate of deterioration between 224 AD patients with and without CVRF, except for cerebrovascular events that were associated with more rapid decline (50). Abellan et al (51) studied 620 AD patients from the REAL.fr cohort. Results found no progression rate difference, neither in MMSE nor ADAS-cog scales, comparing the CVRF group (presence of hypertension, diabetes, hypercholesterolemia at baseline) with the non-CVRF group after 2 years of follow-up. However, these findings are inconsistent with Mielke et al (2007) study. A total of 135 individuals with incident AD, identified in a population-based sample of elderly persons, were followed for a mean of 3.0 years. During each visit the MMSE and CDR were administered. Atrial fibrillation, systolic hypertension, and angina were associated with more rapid decline, while history of coronary artery bypass graft surgery, diabetes, and hypertension medications were associated with a slower rate of decline. An age interaction was found such that systolic hypertension, angina, and myocardial infarction were associated with greater decline with increasing baseline age (52).

A recent meta-analysis has assessed the association of smoking with dementia and cognitive decline. Nineteen prospective studies with at least 12 months of follow-up were included with a total of 26374 participants followed for dementia for 2-30 years. Mean study age was 74 years. Compared with those who never smoked, at baseline, current smokers showed greater yearly declines in MMSE scores over the follow-up period (53).

Genetics factors

Whereas the risk factors mentioned above may be considered as clinical markers for a RCD, genetic factors may be one of the underlying unknown causes of variance in differential rates of decline in AD patients. Two genetic factors have been linked with the rate of progression of AD disease: Apolipoprotein E (4) (ApoE ε4) and the Butyrylcholinesterase (BuChE) genotype.

ApoE genotype predictive value in already diagnosed AD is still controversial. Carriers of ApoE ε4 with mild AD (MMSE score 22 to 26) declined faster on the ADAS-cog over 6 months compared with non-carriers, whereas moderate AD ApoE ε4 carriers (MMSE score 10 to 21) declined slower than those without the allele (54). A recent study showed that ApoE ε4 may influence rate cognitive decline most significantly in the earliest stages of AD (55). However, the many studies have failed to link the presence of ApoE ε4 to rate of progression possibly owing to the fact that it is disease severity dependent (56) and that the rate of cognitive decline fits in non-linear models better (57).

Higher level of BuChE may be associated with an accelerated rate of cognitive decline in AD. The K and A variant of BuChE encode for lower expression or lower activity of the BuChE enzyme in the plasma. Thus, patients possessing these variant alleles are less likely to experience an aggressive course of the disease (58, 59).

Brain imaging

Some authors found a correlation between the rate of brain morphological changes, measured by magnetic resonance imaging (MRI) and the rate of cognitive decline. Jack CR Jr et al, found that the atrophy rates (hippocampus, entorhinal cortex, whole brain and ventricle) were greater among fast than slow AD progressors (60) According to this, Kinkingnéhun et al, in 2008 aimed to determine whether regional atrophy could predict the rate of decline in patients with mild Alzheimer's disease. At the end of 3 years of follow-up, patients were dichotomised into slow decliners or fast decliners based on the basis of their decline in MMSE score over time. Voxel-based morphometry analysis demonstrated that patients, who will have a faster decline at 3 years, already had a more extensive cortical atrophy than slow decliners, especially in the medial occipitoparietal areas, which was not yet detected by clinical and neuropsychological assessment. (61) These data support

the use of rates of change in serial MRI studies in addition to standard clinical/psychometric measures as surrogate markers of disease progression in AD. In addition, it seems that white matter hyperintensity (WMH) volumes are related to cortical atrophy and neuropsychological impairment. (62). Recently, the association between the severity of WMH and baseline MRI measurements of cerebral atrophy with the rate of decline in Columbia modified MMSE was evaluated in 84 AD patients from the Predictors Study. General estimating equation models demonstrated that both degree of cerebral atrophy and severity of WMH are associated with the rapidity of cognitive decline. They suggest that atrophy and WMH may have a synergistic effect on future decline in AD (63).

The regional cerebral blood flow (rCBF) was measured in rapidly and slowly progressing groups of AD patients using single-photon emission computed tomography and was compared between the groups. The rCBF in the right posterodorsal, anterior and superior prefrontal cortices and the inferior parietal cortex was significantly lower in the rapidly progressing patients. Moreover, lower perfusion in these regions correlated significantly with rapid deterioration in the MMSE (64)

Biological markers

Standard markers in cerebrospinal fluid (CSF), as soluble amyloid beta 1-42 (Abeta1-42) and total tau protein (t-tau) may contribute to dementia subtypes diagnostic accuracy. Yet, their sensitivity to assess the different degree of cognitive decline is not clarified. One study showed that CSF markers are not related to the different degree of cognitive impairment (65). Another study showed that CSF measures of Abeta1-42 and t-tau levels by APOE genotype remained stable in AD. These findings may suggest that the soluble Abeta1-42 and t-tau CSF concentration has a negligible correlation with the clinical progression (66). However, a more recent longitudinal study of 122 AD patients followed for a mean of 4.2 (2.6) years, found a relation between plasma biomarkers and the rate of progression of the disease. Low plasma levels of Abeta40, Abeta42, and high-sensitivity C-reactive protein were associated with a significantly more rapid cognitive decline, as indexed using the Blessed Dementia Scale, than high levels. (67)

Therapeutic approaches

The lack of both consensus definition and consensual clinical assessment tools is one of the major barriers for establishing an appropriated management of rapid cognitive decliners in clinical practice. Presently, management of rapid decliners in AD remains to be a challenge waiting to better know predictive factors of a RCD. To date no specific guidelines exist to follow-up or to treat patients with this condition.

Two tested drug therapies have shown a possible effectiveness in patients with RCD: rivastigmine (anticholinesterasic drug with an additional inhibition of BuChE) (16, 17) and memantine (18). A protective effect of all AchEIs was observed in developing an episode of RCD which was defined as a loss of 3 or more points in MMSE in one year (68). Therefore, it remains to be confirmed whether these beneficial effects are caused by the additional inhibition of BuChE by rivastigmine compared to other AChE selective inhibitors.

Discussion

At this moment in time, only 3 studies have aimed to propose a definition of RCD based on their predictive values in different adverse outcomes in AD from cohort populations: “a loss of 3 points or greater in MMSE per year”, “a loss of 4 points or greater in MMSE during 6 months” and “the gain of 7 points or more in the ADAS-cog during six months” (see table 2).

Carcaillon et al, showed a higher risk of mortality in those patients with a lost of ≥ 3 points in MMSE and Soto et al, showed a higher risk of physical dependence with the same threshold of ≥ 3 points in all stages of severity. Concerning mortality and institutionalisation, Soto et al, found that the predictive value of the loss of ≥ 4 points appeared to be significant solely at moderate stages of the disease, depending on the initial MMSE score level. This effect may reflect the limits of the MMSE; it is known that the AD-associated drop in MMSE scores over time is non-linear (3, 5). Although MMSE is a well-accepted instrument to assess level of cognitive function, it has limited value in measuring the progression of AD. The rate of change is substantially less for patients with mild disease or with very severe disease. Also, there exists a strong relationship between baseline severity and the change observed over the next follow-up period (20). Thus, at mild stages of the disease the MMSE presents a poor sensitivity to detect changes and at more severe stages a floor effect appears. Nonetheless, the MMSE is a tool used worldwide due to its brevity, simplicity and applicability across the mild to moderate stages of the disease. This differs from the ADAS-cog, which takes approximately 45 minutes to complete, thus making it less useful for clinical practice.

The REAL.FR cohort does not represent the entire older adult population. Instead, it represents a selected group of AD patients who participate in a follow-up care at specialized AD centres. Whereas, PAQUID population is representative of the older adult population, since it is a longitudinal population-based study with a long-term follow-up, spanning 13 years. PAQUID study design allowed authors to analyse unselected new cases of AD occurring in general population. This cohort provides data on the evolution of cognitive performances over the 13 years of follow-up and thus the cognitive decline before the dementia diagnosis, as well as a long-term follow-up of patients until death. One disadvantage of this process is that patients were visited every two or three years. Therefore, the

annual rate of cognitive decline and the actual date of diagnosis (as they pointed out) may be imprecise.

A 6-month period of time it seems to be a useful interval in clinical practice. The evidenced based benefits of specific AD treatments (AchEIs and memantine) become significant after three and six months. Thus, the time interval to assess pharmacological treatment's efficacy in clinical practice should be at the very least, every 6 months in order to make decisions in relation to the use and modification of these treatments. Several authors have already proposed a 6-month interval regular visit (69, 70, 71, 72, 73). Moreover, regular follow-up every 6 months in a specialised centre seems to be an essential element for better management and for optimisation of the effects of specific AD treatments, obtaining a significantly better clinical outcome in AD patients (3).

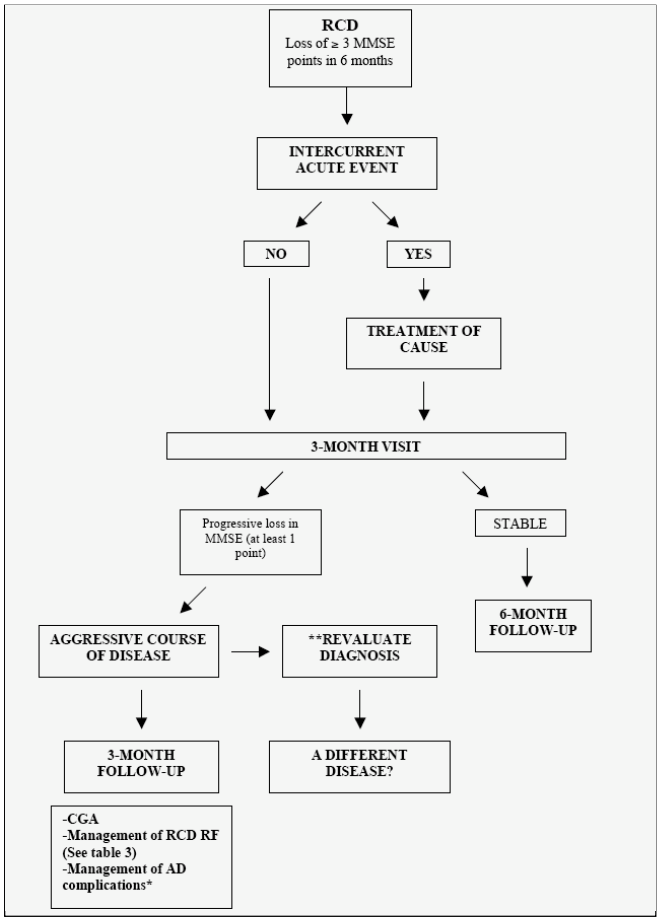
All members of the consensus agreed to choose a threshold of ≥ 3 points loss in MMSE since it showed a predictive value in mortality and in physical dependence. This threshold allows including those patients with a loss of ≥ 4 points presenting a higher risk of institutionalisation and mortality, as well (22).

Rapid cognitive decline may be caused by multiple factors (intrinsic disease factors, associated comorbidities and/or intercurrent acute events). RCD over the course of the disease could possibly be seen as a dynamic condition. Patients that experience an episode of RCD for certain periods throughout the course of the disease could later transit to a slower evolution. However, it has also the potential to become definitely a rapid decliner, with fatal consequences. At the present, in absence of more etiological knowledge, RCD may be considered as a phenomena observed in clinical practice (a significant deterioration on specified dementia assessment scales within a period of time). From this reflection, two types of patients could be considered: those presenting an episode of RCD secondary to an intercurrent acute event, reversible or non-reversible, and those presenting an aggressive course of the disease which could be considered as "primary" rapid decliners. Nevertheless, the different papers evaluating the prognosis of patients presenting an episode of RCD (21, 22), did not take into account in their analyses the possible factors responsible for the RCD observed. Therefore, no matter if they were "primary" rapid cognitive decliners or rapid decliners after a specific cause, both types of patients presented a similar worse evolution in terms of mortality, physical dependence or institutionalisation. In consequence of this and the dynamic condition of the phenomena of an episode of RCD, patients with this condition should benefit for a closer and specific follow up.

Indeed, similarly to cardiovascular disease and CVRF, the dynamic condition of a RCD may translate the existence of two types of risk factors for RCD. Those modifiable risk factors responsible for a reversible RCD after an optimal management, and those non-modifiable ones responsible for a continuous non-reversible RCD. The recognition of these factors would enable practitioners to identify patients at high risk for rapid disease progression and thus, who are in greatest need of intervention. On the basis of the results of different studies mentioned above, several risk factors may partly account for the RCD observed in daily clinical practice (see table 3).

In clinical practice the physician is usually faced to a patient who has just experienced a RCD. In a simple approach three questions should be contemplated: Is it caused by an intercurrent acute even? Is it another entity different than AD? Or does the patient present an aggressive course of AD? See figure 1.

Figure 1
Rapid Cognitive Decline in clinical practice



RCD: rapid cognitive decline; CGA: comprehensive geriatric assessment; RF: risk factors; *AD most common complications: physical dependence, high caregiver burden, malnutrition, and psychological and behavioural symptoms; **If other clinical signs atypical for AD are present

After recognition of the RCD episode, an evaluation should occur so to increase the chances of reversing the condition. For this purpose, a first approach would be to try to identify an intercurrent acute event with a first clinical examination and, if necessary, standard paraclinical investigations. All somatic complications (epilepsy, infectious disease, cerebrovascular

event…), iatrogenic drugs effect, environmental changes (caregiver medical problem, caregiver exhaustion or institutionalisation) may be considered as an intercurrent acute even and cause a RCD.

Once the episode of RCD is established and there is a continuous progressive loss on the MMSE, a re-evaluation of AD diagnoses should be performed, if clinical signs different from AD are present, in order to identify another neurological disease such as Lewy Body dementia or Creutzfeldt Jacobs's disease in between others. After verifying AD diagnoses, a specific and closer follow-up with regular 3-month visits should be proposed since these patients are probably "primary" rapid decliners presenting an aggressive course of the disease with worse prognosis. At each follow-up visit the identification of RCD risk factors should be considered with a special attention to those modifiable ones in order to implement strategies to reduce the effect of this risk factor.

Consensus Statements on Rapid Cognitive Decline

The expert group proposed the following statements:

1) The loss of 3 points or greater in MMSE during six months as a definition of rapid cognitive decline to be used in routine medical practice and to be relevant for clinical-decision making in patients with mild to moderately- severe AD.
2) In the absence of a specific management in RCD an algorithm for the management and follow-up of rapid decliners is proposed (see figure 1).

Future challenges

Untangling the physiopathology leading to an aggressive cognitive course of the disease needs further enquiry. Known, established, and yet to be discovered risk factors, need further assessment so to clarify the pathways of RCD. By doing so, multidisciplinary programs and therapeutic issues can be implemented in order to prevent, delay or avoid adverse consequences associated with a RCD. To do so, specific AD patient cohorts should be designed in order to study RCD along with post mortem evaluation. Additionally, efficacy of new therapeutics and/or management strategies in treating RCD should be evaluated in future clinical trials.

Taking into account the multidimensional aspect of AD, a "rapid decliner" should not be only identified by a fast cognitive progression, but that patient presenting a significant clinical deterioration, within a short period of time, like 6 months, concerning, besides the cognitive status, his functional or psycho-behavioural status.

Acknowledgements: Unrestricted educational grant from NOVARTIS Pharma SAS, Rueil Malmaison, France.

References

1. Holmes C, Lovestone S. Long-term cognitive and functional decline in late onset Alzheimer´s disease: therapeutic implications. Age and Aging 2003; 32: 200-204
2. Folstein MF, Folstein SE, Mc Hugh PR. Mini-Mental-Test: a practical method for grading the cognitive state of patient for the clinician. J Psychiatr Res 1975; 12: 189-198
3. Morris JC, Edland S, Clark C et al. The consortium to establish a registry for Alzheimer´s disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer´s disease. Neurology 1993; 43: 2457-2465.
4. Cortes F, Gillette-Guyonnet S, Nourhashemi F et al. Recent Data on the natural history of Alzheimer disease: Results from the REAL.FR study. J Nutr Health Aging 2005; 9: 86-94
5. Kraemer HC, Tinklenberg J, Yesavage JA. "How far" vs "how fast" in Alzheimer´s disease. Arch Neurol 1994; 51:275–79
6. Hui JS, Wilson RS, Bennett DA et al. Rate of cognitive decline and mortality in Alzheimer´s disease. Neurology 2003;61:1356-1361
7. Dumont C, Voisin T, Nourhashemi F et al. Predictive factors for rapid loss on the Mini-Mental State Examination in Alzheimer´s disease. J Nutr Health Aging 2005; 9:163-167
8. Holtzer R, Wegesin D, Albert S et al. The rate of cognitive decline and risk of reaching clinical milestones in Alzheimer´s disease. Arch Neurol 2003; 60:1137-1142.
9. Doody RS, Massman P, Dunn K. A method for estimating progression rates in Alzheimer's disease. Arch Neurol 2001; 58:449-454
10. O´Hara R, Thompson JM, Kraemer HC et al. Which Alzheimer patients are at risk for rapid cognitive decline? J Geriatr Psychiatry Neurol 2002; 15: 233-238
11. Atchinson TB, Bradshaw M, Massman PJ. Investigation of profile difference between Alzheimr´s disease patients declining at different rates: Examination of baseline neuropsychological data . Arch Clin Neuropsychol 2004; 19:1007-1015
12. Helmer C, Andrieu S, Pérès K, Orgogozo JM, Vellas B, Dartigues JF. Predictive value of decline in ADAS-cog for survival without severe Alzheimer's disease. Dement Geriatr Cogn Disor 2007: 168-174
13. Gauthier S, Vellas B, Farlow M, Burn D. Aggressive course of disease in dementia. Alzheimer's and Dementia. 2006; 2:210-217
14. Dumont C, Gillette-Guyonnet S, Andrieu S, Cantet C, Ousset PJ, Vellas B, groupe REAL.FR. Baisse rapide du Mini-Mental State Examination: etude REAL.FR. Rev Med Int 2003; 24:345s-350s
15. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356-1364
16. Farlow MR, Hake A, Messina J et al. Response of patients with Alzheimer´s disease to rivastigmine treatment is predicted by the rate of disease progression. Arch Neurol 2001; 58:417–422
17. Farlow MR, Small GW, Quarg P, Krause A. Efficacy of rivastigmine in Alzheimer´s disease patients with rapid disease progression: Results of a meta-analysis. Dement Geriatr Cogn Disord 2005; 20:192-197
18. Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2007; 24:138-145
19.- Soto ME, Gillette-Guyonnet S, Vellas B, the REAL.FR group. Rapid cognitive decline: searching for a definition and predictive factor among elderly with Alzheimer´s disease. J Nutr Health Aging 2005; 9: 158-161
20. Clark CM, Sheppard L, Fillenbaum CG, et al. Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer´s disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer´s disease. Arch Neurol 1999; 56:857-862
21. Carcaillon L, Pèrès K, Péré JJ, Helmer C, Orgogozo JM, Dartigues JF. Fast cognitive decline at the time of dementia diagnosis: a major prognostic factor for survival in the community. Dement Geriatr Cogn Disord 2007; 23:439-445
22. Soto ME, Andrieu S, Cantet C et al. Predictive Value of Rapid Decline in Mini-Mental State Examination in Clinical Practice for Prognosis in Alzheimer's disease. Dement Geriatr Cogn Disord 2008;26:109-116
23. Capitani E, Cazzaniga R, Francescani A, Spinnler H. Cognitive deterioration in Alzheimer´s disease: is the early course predictive of the later stages? Neurol Sci 2004; 25:198-204
24. Noda A, MS, Kraemer H, Taylor JL, Schneider B, Ashford JW, Yesavage JA. Strategies to reduce site differences in multisite studies: a case study of Alzheimer disease progression. Am J Geriatr Psyquiatry 2006; 14:931-938
25. Jacobs D, Sano M, Marder K et al. Age at onset on Alzheimer´s disease: relation to pattern of cognitive dysfunction and rate of decline. Neurology 1990; 40:8-14
26. Ho GJ, Hansen LA, Alford MF et al. Age at onset is associated with disease severity in Lewy body variant and in Alzheimer´s disease. Neuroreport 2002; 13:1825-1828
27. Stern Y, Alexander GE, Prohovnik I, Mayeaux R. Inverse relation-ship between education and parietotemporal perfusion deficit in Alzheimer´s disease. Ann Neurol 1992; 32:371-375.
28. Teri L, McCurry SM, Edland SD et al. Cognitive decline in Alzheimer´s disease: a longitudinal investigation of risk factors for accelerated decline. J Gerontol A Biol Sci Med Sci 1995; 50:M49-M55
29. Stern Y, Albert S, Tang MX, TsaiWY. Rate of memory decline in AD is related to education and occupation: Cognitive reserve? Neurology 1999;53:1942-1947
30. Hall CB, Derby C, Le Valley A, Katz MJ, Verguese J, Lipton RB. Education delays accelerated decline on a memory test in persons who develop dementia. Neurology 2007 69: 1657-1664

31. Guk-Hee Suh, Young-Su Ju, Byeong Kil Yeon, Ajit Shah. A longitudinal study of Alzheimer´s disease: rates of cognitive decline and functional decline. Int J Geriatr Psy 2004; 19:817-824
32. Wilson R, McCann J, Li Yan, Aggarwal N, Gilley D, Evans D. Nursing home placement, day care use, and cognitive decline in Alzheimer´s disease. Am J Psychiatry 2007; 164: 910-915
33. Kaufman Y, Anaki D, Binns M, Freedman M. Cognitive decline in Alzheimer´s disease: impact of spirituality, religiosity, and QOL. Neurology 2007 68: 1509-1514
34. Ousset PJ, Nourhashemi F, Reynish E, Vellas B. Nutritional status is associated with disease progression in very mild Alzheimer's disease. Alz Dis Assoc Disord. 2008; 22:66-71
35. Chui HC, Lyness SA, Sobel E, Schneider LS. Extrapiramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer´s disease. Arch Neurol 1994; 51:676-681
36. Miller TP, Tinklenberg JR, Brooks JO, Yesavage JA. Cognitive decline in patients with Alzheimer´s disease: differences in patients with and without extrapiramidal signs. Alzheimer Dis 1991; 5:251-256
37. Lopez OL, Wisnieski SR, Becker JT, Boller F, Dekosky ST.. Extrapiramidal signs in patients with probable Alzheimer´s disease. Arch Neurol 1997; 54:969-975
38. Scarmeas N, Hadjigeorgiou GM, Papadimitriou A et al. Motor signs during course of Alzheimer´s disease. Neurology 2004; 63:975-982
39. Capitani E, Francescani A, Spinner H. Are hallucinations and extrapiramidal signs associated with a steeper cognitive decline in degenerative dementia patients? Neurol Sci 2007; 28:245-250
40. Kraybill MI, Larson EB, Tsuang DW, Teri L. McCormick WC, Bowen JD et al. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. Neurology 2005; 64:2069-2073
41. Marra C, Silveri Maria C, Gainotti G. Predictors of cognitive decline in the early stage of probably Alzheimer´s disease. Dement Geriatr Cogn Disord 2000; 11:212-218
42. Buccione R, Perri R, Carlesimo A, Fadda L, Serra L, Scalmana S, Caltagirone. Cognitive and behavioural predictors of progression rates in Alzheimer´s disease. European Journal of Neurology. 2007; 14:1468-1331
43. Shaufele M, Bickel H, Weyerer S. Which factors influence cognitive decline in older adults suffering from dementing disorders?. Int J Geriatr Pychiatry 2002;17:1055-1063
44. Coen RF, Maguire C, Swanwick GR, Kirby M, Burke T, Lawlor BA, et al. Letter and category fluency in Alzheimer´s disease: a prognosis indicator of progression. Dementia 1996;7:246-250
45. Beatty WW, Salmon DP, Tröster AI, Tivis RD. Do primary and secondary measures of semantic memory predict cognitive decline in Alzheimer´s disease? Aging, Neuropsychology, and Cognition 2002; 9:1-10
46. Wilson RS, Tang Y, Aggarwal NT, Gilley DW, McCann JJ, Bienias JL, Evans DA. Hallucinations, cognitive decline, and death in Alzheimer´s disease. Neuroepidemiology 2005;26:68-75
47. Mortimer JA, Ebbit B, Jun SP et al. Predictors of cognitive and functional progression in patients with Alzheimer´s disease. Neurology 1992; 42:1689-1696
48. Scarmeas N, Brandt J, Blacker D et al. Disruptive behavior as a predictor in Alzheimer Disease. Arch Neurol 2007; 64 1755-1761
49. Bhargava D, Weiner M, Hynan L, Diaz-Arrastia R, Lipton A. Vascular disease and risk factors, rate of progression, and survival in Alzheimer´s disease. J Geriatr Psychiatry Neurol 2006;19:78-82
50. Regan C, Katona C, Walker Z, Hooper J, Donovan J, Livingston G. Relationship of vascular risk to the progression of Alzheimer disease. Neurology 2006;67:1357-1361
51. Abellan G, Rolland Y, Nourhashémi F, Cantet C, Andrieu S, Vellas B. Cardiovascular risk factors and progression of Alzheimer´s disease. Alz Dis Assoc Disord. In press
52. Mielke MM, Rosenberg PB, Tschanz J et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007; 69:1850-1858
53. Anstey KJ, von Sanden C, Salim A, O´Kearney R. Smoking as a risk for dementia and cognitive decline: a meta-analyses of prospective studies. Am J Epidemiol, 2007;166:367-378
54. Lane R, Farlow M. Lipid homeostasis and apolipoprotein E in the development and progression in Alzheimer´s disease. J Lipid Res 2005;46:949-968
55. Consentino S, Scarmeas N, Helzner E et al. APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology, 2008; 70:1842-1849
56. Holmes C. Genotype and phenotype in Alzheimer´s disease. Br J Psy 2002;180:131-134
57. Martins CAR, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer´s disease. Neurology 2005; 65:1888-1893
58. Holmes C, Ballard C, Lehman D, David S, Beaumont H, Day IN, et al. Rate of progression of cognitive decline in Alzheimer´s disease: Effect of butyrylcholinesterase K gene variation. J Neurol Neurosurg Psychiatry 2005; 76:640-643
59. O´Brien KK, Saxby BK, Ballard CG et al. Regulation of attention and response to therapy in dementia by butyrylcholinesterase. Pharmacogenetics 2003; 13: 231-239
60. Jack CR Jr, Shiung MM, Gunter JL, et al RC. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology. 2004 24; 62:591-600
61. Kinkingnéhun S, Sarazin M, Lehéricy, Guichart-Gomez E, Hergueta T, Dubois B. VBM anticipates the rate of progression of Alzheimer disease: a 3-year longitudinal study. Neurology 2008; 70:2201-2211
62. Capizzano AA, Acion L, Bekinschtein T, Furman M, Gomila H, Martinez A, Mizrahi R, Starkstein SE. White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2004 Jun;75(6):822-7.
63. Brickman AM, Honig LS, Scarmeas N et al. Measuring cerebral atrophy and white matter hyperintensity burden predict the rate of cognitive decline in Alzheimer disease. Arch Neurol. 2008;65:1202-1208
64. Nagahama Y, Nabatame H, Okina T et al. Cerebral correlates of the progression rate of the cognitive decline in probable Alzheimer's disease.Eur Neurol 2003;50:1-9
65. Stefani A, Martorana A, Bernardini S et al. CSF markers in Alzheimer disease patients are not related to the different degree of cognitive impairment. J Neurol Sci. 2006; 251:124-128
66. Huey ED, Mirza N, Putnam KT, et al. Stability of CSF beta-amyloid (1-42) and tau levels by APOE genotype in Alzheimer disease patients. Dement Geriatr Cogn Disord. 2006; 22:48-53
67. Locascio JJ, Fukumoto H, Yap L et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease; Arch Neurol; 2008; 65:776-785
68. Gillette-Guyonnet S, Andrieu S, Cortes F, et al. Outcome of Alzheimer's disease potential impact of cholinesterase inhibitors. J Gerontol A Biol Sci Med Sci. 2006; 61:516-20
69. Fillit HM, Doody RS, Binaso K, Crooks GM, Ferris SH, Farlow MR, Leifer B, Mills C, Minkoff N, Orland B, Reichman WE, Salloway S. Recommendations for best practices in the treatment of Alzheimer's disease in managed care. Am J Geriatr Pharmacother 2006; 4 Suppl A:S9-S24
70. Nourhashémi F, Gillette S, Andrieu S. Managing Alzheimer's disease: global care and support program. Rev Prat. 2005; 55: 1903-1911
71. California Workgroup on guidelines for Alzheimer's Disease Management. Guidelines for Alzheimer's disease management. 2002
72. Cummings JL, Frank JC, Cherry D, Kohatsu ND, Kemp B, Hewett L et al. Guidelines for managing Alzheimer's disease: part II. Treatment. Am Fam Physician 2002; 65: 2525-2234
73. NICE: National Institute for Health and Clinical Excellence. Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease (amended); September 2007. Available at: http://www.nice.org. uk/guidance/index.jsp?action=download&o=36556
74. Masse I, Border R, Deplanque D, Al Khedr A, Richard F, Libersa C, Pasquier F. Lipid lowering agents are associated with a slower cognitive decline in Alzheimer´s disease. J Neurol Neurosurg Psyquiatry 2005; 76:1624-1629