PREVENTION OF PROGRESSION TO DEMENTIA IN THE ELDERLY: RATIONALE AND PROPOSAL FOR A HEALTH-PROMOTING MEMORY CONSULTATION (TASK FORCE MEMBERS)

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Abstract: Alzheimer’s disease (AD) is the most frequent form of dementia and according to the most recent estimation it affects nearly 27 million people in the world. The onset of the disease is generally insidious. It is becoming increasingly evident that the underlying pathophysiological mechanisms are active long before the appearance of the clinical symptoms of the disease. In the current context, it is important to develop strategies to delay the onset of cognitive decline. Delaying the onset by 5 years would reduce the prevalence by half at term, and a delay of 10 years would reduce it by three-quarters. The effectiveness of currently suggested preventive approaches remains to be confirmed, but certain strategies could be applied straight away to at-risk subjects. We propose that a health-promoting memory consultation should be set up for elderly persons who have attended a specialized memory consultation and in whom the diagnosis of dementia and of AD in particular, has not been established by standardized tools. Through this consultation, they would be offered full multidimensional investigation of all aspects of their health status, follow-up could be organized, general practitioners in private practice could be made more conscious of this population and the elderly could be made more aware of the risk factors to which they are exposed. The development of an information policy for the elderly would meet a present need. In our reflection, we must take into account the question of how to give this preventive consultation its due place in the healthcare pathway of the elderly person in order to ensure coordinated follow-up with all the other health professionals involved. The principle of the health-promoting memory consultation is undergoing validation in a large French multicentre preventive trial in 1200 frail elderly persons aged 70 years followed for three years, the Multidomain Alzheimer Preventive Trial (MAPT).

The ageing of the population which affects all developed countries is leading to an increase in age-related diseases, led by the dementias, notably Alzheimer’s disease (AD). At the present time, AD accounts for 70% of prevalent dementias. Its incidence is increasing markedly and according to current predictions the number of persons affected will double every twenty years (1). In their recently published study, Brookmeyer et al. (1) estimated the number of Alzheimer patients worldwide in 2006 to be 26.6 million (ranging between 11.4 to 59.4 million according to the geographical area considered). Their forecast for the future indicates that this number could be multiplied by four by 2050 and reach 106.8 million (variation of 47.2 to 221.2 million), affecting one in 85 persons. In Europe, the prevalence estimated at 7.21 million in 2006 could reach 16.51 million in 2050. The prevalence rate of the disease at ages 65, 75 and 85 years has been estimated at 0.9%, 4.2% and 14.7%, respectively. In France, the figures obtained at the 10-year follow-up of the French Paquid cohort showed that the prevalence of AD in subjects aged 75 and over was estimated at 17.8% (2). Various population studies have estimated the prevalence of AD according to age and sex (3). Extrapolation of these data to the 2004 census gives an estimated figure in France of 766 000 persons with dementia aged over 75 years, of whom over two-thirds are women (618 000) and persons aged over 85 years (394 000). The Eurodem data make it possible to advance figures for each age group, with a mean annual incidence rate which shows a marked increase from 2 per 1000 persons between the ages of 65 and 69 years to 70 per 1000 after 90 years (4). In metropolitan France, the number of new cases of dementia each year is estimated at 225 000 (Paquid data) (5). In persons aged over 85 years, prevalence ranges from 15 to 40% while annual incidence ranges between 60 and 100 person-years (6).

The onset of AD is generally insidious. It appears increasingly evident that the underlying pathophysiological mechanisms are active long before the appearance of the clinical symptoms of the disease. Disease progression does not consist only of memory loss; it also affects the physical condition and independence of the patient, as well as the health of the caregiver. In the absence of curative treatments,
Alzheimer disease in the elderly: is progression accessible to prevention?

A relation can be established between the specific lesions - senile plaques and neurofibrillary degeneration (NFD) - and clinical expression of AD. It should however be noted that only the distribution and extent of NFD are correlated with the type and gravity of the symptoms, respectively. The preferential involvement of certain cortical regions (parietotemporal regions) and of certain neuromediator systems (the cholinergic and glutamatergic systems) is as yet unexplained. The lesions develop slowly and progressively. The senile plaques are diffusely distributed; on the other hand, the distribution of NFD follows a precise course, involving first the entorhinal cortex and the hippocampal-amygdala region, then the temporoparietal and frontal cortex, before finally affecting most of the cortical and subcortical zones. Compensatory processes (complementary memory systems, activation of neurotransmitters and of other neuronal networks) ensuring maintenance of cognitive reserve make it possible to prevent clinical expression of the lesions at the beginning of the disease and so delay the appearance of disease symptoms (9). AD may thus develop in three phases: an asymptomatic phase of unknown duration, a pre-dementia phase during which the first signs of moderate cognitive decline appear, and a dementia phase.

The term of mild cognitive impairment (MCI) has been proposed to describe subjects who present moderate but significant cognitive alteration which may worsen within two years. Clinical criteria for the definition of MCI have been proposed by Petersen et al. (10): a memory complaint confirmed by those close to the patient, objective memory impairment, normal general cognitive function, intact activities of daily living and absence of dementia. This concept is particularly important as the conversion rate of MCI to dementia is high (11-12). Lehner et al. (13) observed an annual conversion rate to AD of 6.5% in a population of elderly persons with memory complaints. The conversion rate was particularly high - about 20% - in subjects with amnestic MCI, whereas it was 3% in subjects with a subjective memory complaint but in whom no memory deficit was revealed by neuropsychological tests. Numerous studies have also suggested that memory complaints could be an early indicator of cognitive deterioration which is at a stage still undetectable by standard neuropsychological tools (14-18). The prevalence of memory complaints – defined as everyday memory problems – in the aged ranges between 25 and 50% (19). It is very dependent on the evaluation tools and on the definition used to characterize the complaint. Evaluation of the complaint can be summarized in a simple question « do you think that you have a problem with your memory ? » (20), or specific tools may be used (21). Memory complaints are closely associated with depressive symptoms. Correlations have also been found between memory complaints and changes in brain morphology, in particular left hippocampal volume (22) or white-matter lesions (23). Moreover, memory complaint may be a risk factor for cognitive decline (14,17, 24-26), AD or dementia (27-35). A memory complaint spontaneously expressed to the general practitioner or during the memory consultation could be an even more reliable predictor of future cognitive decline than a complaint which did not result in a consultation (29). The Paquid study, carried out in the general population in persons aged 65 years and over at inclusion, has in fact shown that elderly persons who express a memory complaint to their general practitioner have a higher risk of developing dementia than normal subjects who do not express a complaint, whether their cognitive performances are normal (RR=3.26, p=0.05) or
**The search for modifiable risk factors is a major challenge for epidemiological research on the etiology of AD. At the present time, this field is dominated by research on lifestyle factors, in particular vascular risk factors (hypertension, diabetes, lipid disorders), and studies on nutrition have increased. Other approaches are also being explored, such as the role of the patient’s medical history or exposure to certain environmental factors. Increasing attention is being paid, not to the characteristics of the subjects in the years preceding diagnosis, but in a more global manner to the subject’s entire life and in particular to the midlife period towards the age of 50 years (52, 53).**

**Sociodemographic and lifestyle factors**

A low educational level is often associated with an increased risk of developing AD in cohort studies (54). Subjects with a high educational level may have a greater cognitive reserve capacity, allowing later expression of the disease (55). It would seem, moreover, that the effect of educational level is manifested well before the disease is diagnosed, with an increased risk of conversion to the MCI stage for normal subjects with a low educational level (56).

A role of certain lifestyle factors has been suggested, including tobacco consumption (57, 58) as a risk factor and moderate alcohol consumption [59, 60], physical exercise (61), a broad spectrum of relationships or social activities (52, 53) or the practice of intellectual or other activities (52, 53, 62-64) as potentially protective factors.

Recent longitudinal studies carried out in the general population aged 65 years or older have reported an inverse association between regular and sustained physical activity and the onset of cognitive decline or dementia (65-70). However, interventional studies are uncommon and rarely select a cognitive outcome to study the efficacy of standardized physical activity.

Numerous studies have suggested the protective role of varied social contacts and activities, whether intellectual or not (for example reading, games, dancing, gardening, do-it-yourself, travelling, learning a language) on the decline of cognitive function, MCI or the onset of dementia (52, 53, 62-64). However, we should not underestimate the fact that there may be a behavioral change in subjects in the predementia phase (72) which could lead to overestimation of the effect of these factors. It is still difficult to quantify social activities and social networks in epidemiological studies. Marital status could be a good marker of the size of the social network, as is shown by studies which have revealed an increased risk of AD in persons who live alone or who have never married (4, 73, 74).

Similarly, the feeling of solitude defined as perceived isolation or the feeling of being unconnected to other people has recently been associated with increased risk of AD (75). Here again, there are few interventional studies. The long-term efficacy of a standardized cognitive training programme, in particular on the targeted domains, and on independence in instrumental activities of daily living has been demonstrated in a single randomized trial in 2832 elderly persons aged 65 to 94 years (62, 76). The programme offered included memory training sessions, training in reasoning (problem-solving ability) or speed of information processing according to the randomized groups.

**Frailty factors**

Frailty is a new concept which is becoming increasingly important and has arisen both from the clinical care given to elderly persons and from research on ageing. In the 80s, frailty was associated with incapacity, chronic disease, extreme age or the need to call upon geriatric services. At the present time, frailty is dissociated from the other concepts (77). The term of
« frailty » is often used with reference to vulnerable aged persons, who are not capable of withstanding stresses such as disturbances in their environment, injury or acute diseases. These stresses risk leading to a vicious circle in which the elderly person does not succeed in recovering and regaining his or her previous state of health. Physical and/or psychosocial handicaps seem to be the main factors of frailty in aged subjects.

In their studies, Fried and collaborators contributed to the determination of the principal characteristics of frailty: weakness, low endurance, reduced physical activity, slow walking speed and involuntary weight loss (78, 79). These authors also demonstrated that the frail elderly had a higher risk of falls, developing functional limitations and impaired mobility, hospitalization and death within three years. More recently, Buchman et al. (80) showed that elderly persons defined as frail according to Fried’s criteria were at greater risk of AD. There is, moreover, increasingly strong evidence linking walking speed and cognitive decline (81-83). In particular, Alfaro-Acha et al. (83) showed an increased risk of cognitive decline in the elderly subjects who took the most time to walk a distance of 2.4 meters (results of the EPESE study of 2070 subjects aged 65 years and over followed for 7 years). Lastly, some authors have also suggested that weight loss may precede the diagnosis of AD (84-87). Low BMI may be an early sign of disease onset (88). A study of 918 clergymen followed for 5.5 years showed that an annual loss of one BMI unit was associated with a 35% increase in the risk of AD (89).

Other multidomain approaches have been developed to define frailty and have led to the development of a frailty index. These take into account the level of dependence (90, 91) or the deficits identified during clinical examination such as sensory disturbances, urinary problems or cardiovascular risk (91). Incontinence in particular is a known factor of social isolation and depression (92) and it is also frequently reported in elderly persons with cognitive and functional decline (93). It is important to take problems of sight and hearing into account, as they can lead to restriction of social and intellectual activities which in themselves accelerate the trajectory of aging. According to the findings of the French Acouedm study, the risk of developing cognitive disturbances was twice as high in elderly persons with hearing difficulties (94). The findings of the Blue Mountains Eye Study (3509 subjects aged 50 years and over) also showed that persons with moderate to severe visual or hearing impairment had lower MMSE scores (95). The data of the SOF study (Study of Osteoporotic Fractures), concerning 6112 women aged 69 years and over, found that visual impairment on inclusion was associated with cognitive and functional decline during follow-up. The presence of both visual and hearing impairment increased these risks (96). Near vision impairment was also associated with cognitive decline in 2140 subjects aged 65 years and over followed for 7 years in the EPESE study (97). Lastly, some works have suggested a possible association between cognitive impairment and age-related macular degeneration in elderly subjects (98-100).

Changes on the scale of instrumental activities of daily living (IADL) (101) could identify the frail elderly, in particular those with mild cognitive impairment, as shown by Nourhashemi et al. (102). The IADL assesses the subject’s ability to carry out certain complex tasks of daily living (using the telephone, shopping, preparing meals, doing housework and washing, taking medication, managing paperwork and using transport). These authors studied the EPIDOS cohort (EPIDémiologie de l’Ostéoporose), a population of 7500 women volunteers, aged over 75, living at home and free of dementia. Dependence evaluated with the IADL scale was found to be independently associated with numerous characteristics of the frailty syndrome such as isolated memory deficit, vision and hearing impairments, fear of falling and perceived poor health. With the present state of knowledge and in the absence of validated evaluation tools, walking speed appears to be the most pertinent marker of frailty in these subjects according to the recent conclusions of a group of experts (77).

Nutritional factors
Current epidemiological data are in favour of a protective role of certain micronutrients (group B vitamins related to homocystein metabolism, the antioxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids) and macro-nutrients (fish) in the prevention of cognitive decline and dementia (103). Some disagreements exist however between the studies, mainly arising from methodological problems (confounding factors taken into account, mode of collection of nutritional data, forms and doses of the vitamins used in randomized controlled studies). At the present time, it is still difficult to propose specific recommendations for the prevention of AD (103). Moreover, recent findings show that subjects with AD already have inadequate nutrient intakes (calcium, iron, zinc, vitamin A, omega-3 and omega-6 unsaturated fatty acids) in the early stages of the disease (104). Epidemiological analysis of the relations between nutrient consumption and cognitive decline is complex and it is highly unlikely that a single component plays a major role. We need to pursue studies which will improve our knowledge of the biochemical mechanisms underlying the pathophysiological processes and will identify potential therapeutic agents, and which in a public health perspective will examine food groups and dietary patterns. A recently published paper, based on the findings of the French Three Cities study, suggested that a diet with little variety may increase the risk of dementia (105). In this work, daily consumption of fruits and vegetables was associated with reduced risk of dementia. Weekly consumption of fish was associated with reduced risk of AD and dementia only in ApoE epsilon 4 noncarriers. Regular consumption of oil or fish rich in omega-3 fatty acids was associated with reduced risk of dementia, whereas regular consumption of oils rich in omega-6 fatty acids increased this risk. Another study has shown decreased risk of AD in subjects with a diet similar to the Mediterranean diet (106). The outcome of patients with AD
once the diagnostic has been established also appears to be better in patients whose diet is similar to the Mediterranean diet (107).

All these works highlight the need to consider the interactions between micro- and macronutrients in future studies. The impact of classic social determinants of diet, such as regional cultures, social status and educational level, must of course be taken into account. Communication and nutritional advice will benefit from being adapted to dietary habits and to the patient’s stage in the cycle of ageing (108-110).

Vascular risk factors

The relation between blood pressure and dementia is a complex one. Depending on the period of life considered, the effects of blood pressure and of hypertensive treatment differ (111). Nearly all studies report an association between high blood pressure 20 to 30 years before cognitive evaluation and later decline in cognitive function or onset of dementia. In studies where blood pressure was measured at a later period, results are contradictory depending on whether cognitive decline or dementia incidence are examined. One study performed in subjects aged over 75 years found an increased risk of AD in both subjects with the highest systolic values and in those with the lowest values in relation to the median tertile (112). In the same cohort, blood pressure declined during the 3 years preceding the diagnosis of dementia (113). The results of randomized studies with protocols whose primary aim was not to study the effect of blood pressure on dementia or cognitive decline are still too limited. The first randomized Syst-Eur trial with an antihypertensive medication (nitrendipin) showed decreased incidence of dementia in elderly subjects with isolated systolic hypertension (114). The Progress study (115) reported a significantly reduced risk of cognitive decline in subjects treated with perindopril or indapamid. No significant effect on the MMSE score or on change in this score was found in subjects with arterial hypertension treated with candesartan (116).

Longitudinal studies show that diabetes affects cognitive decline or the onset of dementia. In 2006, a review of the literature (117) summed up studies involving nearly 110 000 subjects: the risk of dementia was multiplied 1.5 to 2-fold in diabetic patients compared with non-diabetic patients after adjustment for other cardiovascular risk factors. In addition, studies of the relation between diabetes and cognitive function have revealed a dose-effect relationship (increased duration of disease or more severe disturbances of glycoregulation resulted in poorer cognitive performances) and an improvement in cognitive function when glycemic balance was also improved (118-120). The pathophysiological explanations are multiple. On the one hand, like the other complications of diabetes, chronic hyperglycemia could have damaging effects on the brain in particular via the polyol and hexosamine pathways, via imbalance of the production and degradation of free radicals, or via advanced glycation of functional and structural proteins (121-124). On the other hand, as suggested by Suzanne Craft and collaborators’ work, cognitive alterations are potentially due to the effects of insulin resistance and peripheral hyperinsulinemia via an increased level of free fatty acids and of inflammation markers such as TNF-alpha (125-126). The consequences are low insulin levels in the brain and increased beta amyloid deposits, both of which lead to deterioration of cognitive performances. Treatments which correct the insulin deficiency of the brain, such as inhaled insulin, or which increase sensitivity to insulin, such as PPAR-gamma nuclear receptor analogues, may improve cognitive function (127-128). Furthermore, recent studies report an increased risk of cognitive decline (129-131) and AD (132) in elderly subjects with metabolic syndrome.

Studies on cholesterol levels, decline of cognitive function and dementias are also contradictory (133). High cholesterol levels in middle age may be the most strongly associated with increased risk of AD. Randomized trials of various statins against placebo have so far yielded negative results (134-136).

The implication of vascular factors is also suggested by the results of studies showing a positive relation between obesity and the risk of dementia onset (137-140). The various vascular risk factors must be simultaneously assessed in order to establish scores for dementia risk, as for cardiovascular disorders. This approach has been proposed by Kivipelto et al. [141]. Their aim was to develop a simple method of dementia risk prediction in the elderly based on their vascular risk profile 20 years earlier. Their work was based on the CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study data and concerned 1409 subjects who were first seen in 1977 (mean age 50 years, range 39 to 64 years) and seen again 20 years later in 1998 (mean age 71 years, range 65 to 80 years) to identify dementia. The score which was used, which had a sensitivity of 77% and a specificity of 63%, included age, educational level, hypertension, high cholesterol levels and obesity but not physical activity or apolipoprotein E4.

Mood disturbances, sleep disturbances and other disorders

A review of the literature and a recent meta-analysis suggest that depression could be an independent risk factor for AD (142). A study carried out in 281 subjects aged 65 years and over, with little or no cognitive impairment (evaluated with the Short Portable Mental Status Questionnaire: 4 or less errors) showed however that depressive symptoms are neither prodromal nor predictive of cognitive decline, but that these two states develop concurrently (143).

An association between sleep disturbances (less effective sleep, difficulty in falling asleep, more frequent daytime naps, sleep apnea syndrome) and cognitive decline has been found in several studies (144-148). Among patients with sleep disturbances, the risk of cognitive decline may be greater in ApoE epsilon 4 carriers (149). Sleep disturbances may also be associated with poorer physical performance in elderly women (150). Some studies have underlined the possible association...
between various heart diseases, in particular atrial fibrillation (151), heart failure (152-154) and coronary artery disease (155), and cognitive impairment or AD.

Lastly, other factors (head injuries, aluminium content of drinking water, anesthetics...) have been suggested but their association with AD is based on debatable findings.

The search for potentially modifiable risk factors is a major public health challenge in AD. Our present state of knowledge is inadequate and calls for new projects to be proposed in order to evaluate the impact of factors associated with lifestyle or modified by medical treatments (antihypertensives, management of diabetes).

The health-promoting memory consultation: what population should be targeted and what evaluations should be proposed?

An increasing number of elderly persons attend memory consultations because of memory complaints. In some, dementia or MCI may be diagnosed during the consultation, but in others the complaint may be subjective. This subjective complaint is not necessarily accompanied by objective assessment of impairment of memory or cognitive performance, and so follow-up or interventions are rarely offered. These specialized consultations give us the opportunity to offer follow-up and multidimensional preventive interventions to patients at high risk of developing dementia, in particular dementia of Alzheimer type (the frail elderly with slow walking speed or limitations in instrumental activities of daily living; elderly persons with a high metabolic and vascular risk; elderly persons who express a memory complaint or who present mild cognitive impairment). Follow-up consultations may be proposed on a annual basis, or on a six-monthly basis for elderly persons with mild cognitive impairment. Such management could be included as part of the creation of a health-promoting memory consultation. This initiative would make it possible overall to carry out full multidimensional investigation of the elderly person’s state of health, to organize follow-up and management of the medical problems identified in collaboration with the general practitioners in private practice, to increase the awareness of these physicians of this population, to make the elderly more conscious of the risk factors to which they are exposed, and to undertake effective long-term preventive action. The frequency of the evaluations proposed during follow-up will depend on the initial global evaluation and on the patient’s age. Health-promoting memory consultations should also provide an opportunity to make the elderly more aware of the benefit of certain eating habits (according to the recommendations of the National Plan for Nutrition and Health), of a healthy lifestyle (physical exercise in particular) and of correction of vascular risk factors, which are all parameters that can contribute to the prevention of AD. Education will be a major element in the management of the elderly. Moreover, diagnosis of AD during follow-up will be simplified if the physician is already in possession of a previous neuropsychological evaluation. Preventive interventions directed at modifiable environmental factors are of particular value and should be developed in order to promote healthy ageing. The impact of such actions will be even greater if they are started early. Multidisciplinary management associating the general practitioner, the geriatrician and the neurologist is probably one of the keys to optimal preventive management in the elderly.

Based on the data of the literature, we suggest that the following information should be collected and the following evaluations included in the health-promoting memory consultation:

- sociodemographic information (age, sex, living arrangements, marital status, educational level, professional activities)
- general clinical examination (cardiopulmonary, abdominal, neurological investigations, examination of the limbs, incontinence)
- medical history and concomitant diseases
- polymedication
- sight testing (questioning, test of visual acuity, Amsler grid)
- hearing tests (questioning, hearing handicap inventory for the elderly- screening version (HHIE-S), audiometry)
- assessment of gait and balance disturbances (one-leg balance test, falls) and of frailty (Short Physical Performance Battery, SPPB)
- evaluation of independence (Instrumental Activities of Daily Living (IADL))
- evaluation of nutritional status (Mini Nutritional Assessment, MNA)
- evaluation of depression (history, Geriatric Depression Scale (GDS)-15 items)
- evaluations of metabolic status and cardiovascular risk.

Cognitive function is evaluated during the specialized memory consultation and so it is not included in the initial health-promoting memory consultation. It may be proposed during follow-up and should include evaluations of:

- the memory complaint (visual analogic scales)
- memory deficit (5-word test)
- visual constructive apraxia (clock-drawing test)
- as well as global cognitive evaluation (MMSE).

The expert group discussed the usefulness of including apolipoprotein E epsilon4 allele genotyping in the consultation, but this proposal was not retained. Numerous teams have confirmed that the apolipoprotein E epsilon4 allele is two to four times more frequent in Alzheimer patients than in the general population, whereas the epsilon2 allele seems to have a protective effect. The apolipoprotein E epsilon4 allele is thus an important risk factor for AD. However, at the individual level, the presence of an epsilon4 genotype is insufficient to affirm the diagnosis since not all persons possessing this allele
develop AD. Such an approach thus cannot ignore the ethical questions raised by an attitude which would be equivalent to imposing a diagnosis of AD on the persons concerned and on their families, whereas in the present state of our knowledge the justification for treatment, at least on a medical level, is still insufficient.

Development of an information policy for the elderly would respond to current needs; recent findings have shown that elderly persons feel less concerned by dementia than younger ones, and that they have poor awareness of risk factors (156). The health-promoting memory consultation is being validated as part of a large French multicentre preventive study of 1200 frail elderly persons aged 70 years and followed for three years in the Multidomain Alzheimer Preventive Trial study (MAPT). This study aims to examine the efficacy of isolated omega-3 fatty acid supplementation, of multidomain interventions (nutritional advice, cognitive training, physical exercise, social activities) either isolated or in association, on the evolution of cognitive function. As part of the study, the intervention is carried out every year in the elderly persons receiving the multidomain intervention.

Table 1
Proposal for introducing the health-promoting memory consultation in the healthcare pathway of the elderly person

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References


RATIONALE AND PROPOSAL FOR A HEALTH-PROMOTING MEMORY CONSULTATION


