Is it possible to prevent dementia?
É possível prevenir o desenvolvimento da demência?

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Abstract It is a robust trend that the World's population is growing older. The proportion of elderly compared to other age groups and especially the number of oldest old, above age 85 years, is steadily increasing. One of the most common disorders in later life is dementia, the major cause of functional disability and the need for long-term care. This has prompted intensive research towards identifying risk factors associated with dementia. For current therapeutic intervention of incipient dementia and future prevention trials it is important to identify subjects at high risk of developing dementia. This article reviews clinical and biological findings of the quest to identify pre-dementia in subjects with mild cognitive impairment. It gives an overview of the present knowledge in this area and discusses strategies that may be useful in delaying the onset of dementia.

Keywords Cognition disorders. Memory disorders. Dementia. Alzheimer disease. Risk factors. Primary prevention.

Resumo *A população mundial está envelhecendo. A proporção de idosos cresce de forma constante quando comparada a outras faixas etárias, particularmente para o grupo com 85 ou mais anos de idade. Um dos problemas de saúde mais freqüentes em fases tardias da vida é a demência, uma das principais causas de perda da capacidade funcional em idosos que, com freqüência, requer assistência com cuidados básicos em longo prazo. Como conseqüência, várias pesquisas têm procurado estabelecer os fatores que aumentam o risco de demência. Do ponto de vista terapêutico, é importante ser capaz de identificar de forma confiável indivíduos com alto risco de desenvolver demência, já que esses pacientes seriam o principal alvo de intervenções clínicas desenhadas com o objetivo de preveni-la. Este artigo tem o objetivo de rever os principais achados clínicos e biológicos das pesquisas que tiveram como objetivo identificar "pré-demência" em pessoas com "comprometimento cognitivo leve". O artigo oferece uma visão panorâmica do conhecimento atual nessa área e discute estratégias que podem ser capazes de retardar o início do processo demencial.*

Descritores *Transtornos cognitivos. Transtornos da memória. Demência. Doença de Alzheimer. Fatores de risco. Prevenção primária.*

Introduction

The world's elderly population has been growing at a rate of 2.4% per year during the past decade and in the year 2000 there were already 580 million people aged 60 years or older.[1] With the increasing number of older adults, age-related diseases are also on the rise, particularly degenerative conditions such as dementia. A dementia syndrome is characterised by deterioration from premorbid levels in multiple cognitive domains of sufficient severity to interfere significantly with activities of daily living. In 1995, 1,805,400 people over age 65 years lived in Australia, of whom 129,600 were diagnosed as being demented. An increase of 254% in the population with dementia over 45 years is estimated for the year 2041, compared to a growth of 40% of the total Australian population.[2] The prevalence of dementia increases exponentially with age —doubling every 5 years after age 60 years, increasing from 1% to 25% in the age group 85 years or over.[3] Dementia accounts for 45% of the costs for all neurological and psychiatric disorders in the elderly and is estimated to cost $690 million in 1993/1994 in Australia. An autopsy study in Australia showed that 45% of subjects with dementia have Alzheimer's disease (AD), followed by vascular dementia and mixed cases.[4] Is there anything we can do to prevent future cases of dementia?

Primary prevention of dementia today: clinically healthy and at risk?

As with other common diseases related to age which are a substantial burden to the health care system, we could

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concentrate on risk factors which are thought to contribute to the development of the disease.

A good example is cardiovascular disease. Screening for the relevant risk factors for cardiovascular disease, like hypertension, nicotine and alcohol consumption, overweight, low exercise, unhealthy diet and elevated lipid levels is a common exercise for general practitioners. This primary prevention approach, even before first signs of the disease are present, has proven successful in decreasing the incidence and prevalence of cardiovascular disease. Could we apply this model to dementia? Are there risk factors for dementia that could be prevented or treated?

The most important risk factors for dementia we know of as for today are old age and a positive family history for dementia. The risk of AD for first degree relatives accumulates up to 33% at age 90.[5] Other strong genetic factors in AD include mutations in the presenilin 2, presenilin 1 and amyloid precursor protein genes located on chromosomes 1, 14 and 21 respectively — they all result in an autosomal-dominant mode of inheritance.[6] The apolipoprotein E (APOE) ε4 allele is viewed as an important genetic determinant of susceptibility to AD with late[7] and early onset.[8] Individuals heterozygous for the ε4 allele have the following odds ratio: ε2/ε4=2.6; ε3/ε4=3.2, compared to the most common ε3/ε3 genotype, whereas individuals homozygote for the ε4 allele have an odds ratio of 14.9 (meta-analysis of clinic/autopsy studies[9]).

APOE is thought to influence the deposition of cerebral beta-amyloid (Aβ), which is associated with AD. Other environmental and medical risk factors include low education and premorbid intelligence,[10] history of head trauma[11] and cardiovascular risk factors.

Cardiovascular disease,[12] hypertension and stroke,[13] diabetes mellitus, peripheral vascular disease, atherosclerosis,[14] and elevated homocysteine levels[15] are all associated with cognitive decline and dementia, especially vascular dementia (VD), the second most common cause after AD in caucasians.

Can any of these risk factors be prevented or treated in the present? Old age, underlying genetic factors and low premorbid intelligence are risk factors currently subject to basic research that cannot be influenced at present. Conversely, low education can be attacked via social intervention, history of head trauma by better safety procedures. Medical risk factors should be treated when detected as it is normally done with risk factors for cardiovascular disease or stroke. This usually does not require additional effort, since the risk factors are overlapping and partly identical between these three common conditions (ie dementia, cardiovascular disease and stroke). However, for dementia prospective population-based risk factor intervention trials with non-demented older adults are needed to reach the same evidence level as currently available for cardiovascular diseases and stroke.

Secondary prevention of dementia today: memory impaired and at risk?

Faced with a large number of older adults already complaining of memory problems or suffering from mild memory deficits, the primary prevention approach comes too late.

In that case could secondary prevention be tried, where a pathological condition is detected early and with successful intervention a progression be prevented? Is prevention of dementia realistically delaying the onset of dementia, perhaps to an extent where the natural life span is reached and future dementia patients would have outlived their disease onset? This approach is already in sight, considering the promising reports on the development of new generations of AD medication with preventive potential, like nerve growth factor (NGF), Aβ peptide vaccination, β-sheet breakers and functional anti-Aβ peptides etc.[16-18]

But for this secondary prevention approach to work, we first need to identify older adults with minor clinical problems before they reach the threshold for dementia. What do we know about this nebulous condition where memory starts to fail, but the symptoms of dementia have not yet set in? This would be the "transitional state" between normal healthy aging and dementia, the pre-dementia phase, where objective mild memory problems (mild cognitive impairment) are already present, but the label of a dementia syndrome would be premature.[19] But the boundary between dementia and the preceding pre-dementia phase is fluid and not as clear-cut as currently diagnostic criteria might suggest.

Mild cognitive impairment (MCI): definition and heterogeneity

Objective mild memory impairment in the elderly, these days named mild cognitive impairment (MCI), describes individuals who show memory impairment, but have no decline in their activities of daily living and are not demented. In fact, it is not a new concept and has a long tradition in German psychiatry.

In 1916 Eugen Bleuler mentioned the psycho-organic syndrome ("Psycho-organisches Syndrom"), describing a common symptom pattern with cognitive and non-cognitive symptoms of chronic brain diseases including mild forms of dementia.[20] Later authors distinguished transient from persistent forms of mild cognitive impairment. Hans Heinrich Wieck introduced the term "Durchgangssyndrome" for mild transient mental disorders of organic origin with a non-specific etiology, variable duration and without clouding of consciousness.[21] Gerd Huber phrased in 1972 the term chronic pseudoneurastenic syndromes ("Chronische pseudoneurasthenische Syndrome") for mild persistent changes of personality and intellectual functions of organic origin, unspecific, but often representing initial stages of dementia.[22]

Now the vague diagnostic category of MCI has experienced a renaissance since new approaches in AD drug development emphasised the importance of an early diagnosis of AD. MCI has been rediscovered as potential prodromal dementia and therefore possible starting point for preventive treatment.

As important as MCI now might be for the modern research approach to AD, as confusing are it's various terms and definitions introduced in the literature over time. Table 1 shows a list of the suggested terms.

These definitions have in common a performance below

Table 1 – MCI: name the problem.

Year	Author	Term
1962	Kral et al[23]	Benign senecent forgetfulness (BSF)
1982	Reisberg et al[24]	Mild cognitive impairment (MCI)
1982	Hughes et al[25]	Questionable dementia (QD)
1986	Cook et al[26]	Age – Associated memory impairment (AAMI)
1989	Blackford et al[27]	Late – Life forgetfulness (LLF)
1989	Blackford et al[27]	Age – Consistent memory impairment (ACMI)
1992	ICD – 10[28]	Mild cognitive disorder
1994	Levy et al[29]	Age – Associated cognitive decline (AACD)
1994	Chiu[30]	Dysmentia
1994	DSM – IV[31]	Mild neurocognitive disorder (MND)
1995	Ebly et al[32]	Cognitively impaired not demented (CIND)
1996	Tierney et al[33]	Memory – Impaired no dementia
1997	Graham et al[34]	Cognitively Impaired no dementia
1998	Am Psychol Assoc[35]	Age – Related cognitive decline (ARCD)
1999	Petersen et al[36]	Mild cognitive impairment (MCI)
2001	Petersen et al[37]	Mild cognitive impairment (MCI)

the age norm on tests of memory (MCI) and / or other cognitive domains (AAMI, AACD, CIND) with preserved general intellectual function and normal activities of daily living.

Beyond these similarities the criteria vary wildly from term to term which makes publications in that area hard to compare. This explains also the wide range of prevalence estimations of MCI in the population. Depending on the criteria used to define MCI estimated prevalence rates can vary in population-based samples of subjects above age 50 years from 5.8% to 18.5%, for AAMI even up to 55.8%.[38,39] No international accepted guidelines or diagnostic criteria exist, but recently published guidelines of the American Academy of Neurology are a first step forward in this direction.[37] These guidelines define MCI as listed in Table 2.

Table 2 - MCI criteria according to the AAN (Petersen et al,[37] 2001).

Memory complaint
Objective memory impairment
Normal general cognitive function
Intact activities of daily living
Not demented

Objective memory impairment in this context is usually defined as scoring at least 1.5 SD below age - and education - matched control subjects on a memory test. MCI subjects typically show a poorly delayed recall performance and frequently can not benefit from semantic cues during learning on a verbal memory test.[36] Prevalence estimates indicate that 17% of older adults (aged 65 years or over) and 30% of the very old (aged 85 years and over) have MCI.[34] Follow-up studies showed that MCI patients develop dementia at a rate of 1% to 30% per year[33,36,40-48] with an average conversion rate of approximately 15% per year (Table 3).

Table 3 - Prospective studies on MCI with conversion rate towards dementia/AD.

Year	Study	Endpoint	N	Follow-up (years)	% of Conversion
1991	Flicker et al[34]	Dementia	32	2.0	66
1996	Grundmann et al[40]	AD	687	3.0	44
1996	Tierney et al[33]	AD	123	2.0	24
1997	Bowen et al[42]	Dementia	21	4.0	48
1997	Devanand et al[43]	Dementia	75	2.5	41
1999	Petersen et al[36]	Dementia	76	4.0	48
2000	Daly et al[44]	AD	123	3.0	19
2000	Lautenschlager et al[45]	Dementia	36	1.4	39
2000	Visser et al[46]	AD	60	2.0	27
2000	Wolf et al[47]	Dementia	27	2.5	30
2001	Ritchie et al[48]	Dementia	27	3.0	11

It is now accepted that subjects who develop neurodegenerative dementia, such as AD, go through a stage of MCI, and in these cases MCI can be viewed as a dementia prodrome. But MCI as a whole is a heterogeneous syndrome in terms of outcome, as not all patients with MCI will develop dementia. In fact, in a prospective study of 60 MCI patients, 38% remained stable and 38% even improved their cognitive scores at follow-up after 2 years.[46]

MCI could, amongst others, represent (1) prodrome neurodegenerative dementia, (2) result of cerebrovascular disease, (3) pseudodementia in functional psychiatric disorders like depression (4), result of other somatic diseases, like cardiovascular diseases (5), drug side effects, (6) stable cognitive impairment after head injury etc.

Mild cognitive impairment (MCI): who has pre-dementia?

For a potential preventive intervention of dementia individuals with highest risk to convert to dementia would need to be identified. Do prospective studies like those listed above provide any information how to identify these individuals within the group of MCI?

Studies on MCI often include potential predictive markers for cognitive decline from various areas, such as genetics, biochemistry and neuroimaging. The apolipoprotein E (APOE) ε4 allele was identified as strong predictor of AD in subjects with MCI.[33,49-51]

Volumetric measurement of the hippocampus and the medial temporal lobe[51] and white matter lesions (WMLs)[47] also seem to predict the later development of dementia. A prospective follow-up study of patients with MCI who developed dementia found that subjects who converted had significantly smaller left medial temporal lobe volumes on MRI than those who remained clinically stable.[51]

Other studies showed that functional brain imaging may have some predictive value (18 F FDG positron-emission-tomography (PET)) when used in the assessment of patients with Down's syndrome, ApoE e4 genotype, members of families with mutations on chromosomes 21 and 14, and MCI.[52] In an autopsy study it could be shown that MCI patients already have an increased load of beta-amyloid (Aβ) in the cortex.[53] Corresponding to this finding Aβ levels in the cerebro-spinal fluid (CSF) were reported to be decreased, as for patients with AD, in MCI subjects who develop cognitive decline and dementia at follow-up.[54]

We found that 85.7% of MCI patients who later convert to dementia have decreased CSF (Aβ) levels.[54] These pre-dementia patients also show AD related abnormalities in their cerebral glucose metabolism as measured by 18 F FDG PET.[45]

MCI subjects who become demented at follow-up, however, had a high frequency of ApoE ε4 (57%) and often volunteered to take part in the study because of a positive family history of dementia (63.9%) – therefore, they were part of a highly selected group patients. However, for a preventive treatment trial of dementia a thorough selection to identify MCI patients with the highest risk would be vital.

Potential markers like those mentioned above could help

with this selection process. Independent from the listed biological and genetic findings a positive family history for dementia[55] and old age[56] remain the two most important predictive factors. But can clinical and neuropsychological information also contribute to risk estimation of conversion to dementia in MCI? Several neuropsychological studies identified deficits in verbal episodic memory, new learning and recent memory in subjects with MCI as the earliest measurable cognitive impairment in pre-dementia AD.[57] The medial temporal lobe (particularly the hippocampus) has been associated in neuroimaging studies to these specific cognitive functions.[51,58] There is now growing evidence that detailed systematic clinical information including questions on the activities of daily living can also be helpful to estimate the risk for conversion to dementia in MCI.

Daly et al[44] and Morris et al[59] showed that a standardized clinical assessment with the Clinical Dementia Rating (CDR) with the patient and a next of kin can identify subgroups within MCI who have a higher risk to convert.

The higher the total box score was within the category CDR=0.5 (equivalent to MCI) the higher the risk. Questions from the categories "judgement and problem solving", "home and hobbies" and "personal care" together with a clinical interview at baseline could predict conversion to AD in 88.6% of individuals with MCI.[44]

In our own pilot study, mentioned above, we found that MCI subjects with three or more positive biological markers (ApoE ε4, low Aβ and high tau in the CSF, reduced cerebral metabolism (PET)) at baseline scored also higher on the CDR (sum of boxes: 2.3) than those with only one positive biological marker at baseline (sum of boxes: 1.6), indicating a greater impairment in their activities of daily living (ADL).[60]

Why diagnosing MCI may be a useful first step to prevent dementia.

It is clear that substantial progress has been made during the last years to gather information that can help identifying subjects at increased risk of developing dementia. This progress will ultimately lead to more precise, internationally accepted diagnostic criteria for MCI. The diagnosis of a pre-dementia syndrome should be established, acknowledging that treatment trials with potential preventive agents need pre-dementia patients to start with. Currently, there are international multicentre treatment trials with MCI patients and cholinesterase-inhibitors under way to investigate if the onset of dementia can be delayed.

Next to specific AD targeting agents, pre-dementia patients could also benefit from treatment trials with potential protective substances where some evidence is emerging from epidemiological studies.[61-64] These substances could include estrogen in postmenopausal women, anti-inflammatory agents, vitamins or lipid-lowering agents.

Preventive strategies for the clinician already available today on a individual basis when counselling MCI patients are management of risk factors which have been linked to AD and cerebrovascular disease, for example ceasing smoking, treating hyperlipidimia, hypertension, heart diseases and encouraging physical fitness, productive activities and mediterranean diet.

Conclusion

Prevention of dementia for the time being means realistically delaying the onset of dementia for as long as possible in patients with mild cognitive impairment. Here the future of preventing dementia has already begun since every general physician can introduce health-promoting management for MCI patients. Also, a new generation of more specific AD targeting agents are not far from entering the clinical trial phase. Therefore, the diagnosis of MCI and the identification of pre-dementia patients not only for research purposes, but in clinical routine, is already an important and concrete contribution in our quest to prevent dementia.

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