

# “Continuum of aging casualty”

## Early detection of dementia and the role of protective and risk factors

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### *El Continuum causal del envejecimiento: la detección precoz de la demencia y el papel de los factores protectores y de riesgo*

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#### RESUMEN

La prevalencia de los trastornos cognoscitivos y de la demencia aumenta con la edad y representa un alto costo para la sociedad y para los servicios de salud. Algunos autores han sugerido un proceso continuo que conduce desde el deterioro cognoscitivo hasta la demencia; con una presentación subsintomática en aquel y florida en ésta. La identificación temprana de uno y otra pareciera reposar en la adecuada valoración de los factores de riesgo y en identificación y promoción de conducta saludables que podrían evitar su presencia

**PALABRAS CLAVES.** Trastornos del Conocimiento (Trastornos cognitivos), Demencia, Factores de Riesgo. Prevención y control, Conductas terapéuticas.

*(Carolina Restrepo, Michael Saling, Kathryn Ellis. El Continuum causal del envejecimiento: la detección precoz de la demencia y el papel de los factores protectores y de riesgo. Acta Neurol Colomb 2010;26:Sup (3:1):52-58).*

#### SUMMARY

The prevalence of cognitive disorders and dementia increases with age and represents a high cost to society and health services. Some authors have suggested an ongoing process that leads from the cognitive impairments to dementia, with a presentation few symptoms on the former and a full clinical form in the latter, as the two extremes of a continuum. Early identification and management of risks or protective factors seems the right way to prevent their presence. Clinicians must promoting healthy behavior as a preventing strategy.

**KEY WORDS.** Cognition Disorders, Dementia, Risk Factors, Prevention & control. Therapeutical Approaches.

*Carolina Restrepo, Michael Saling, Kathryn Ellis. “Continuum of aging casualty” Early detection of dementia and the role of protective and risk factors. Acta Neurol Colomb 2010;26:Sup (3:1):52-58).*

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#### INTRODUCTION

Over the past decades there has been a considerable increase in the number of people with cognitive impairment caused by dementia (1). Almost one

hundred years after Alzheimer’s Disease (AD) was first described, we face a profound and growing incidence of the disease throughout much of the world in people living to their 70’s, 80’s, and beyond (2).

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Recibido: 2/08/10. Revisado: 17/08/10. Aceptado: 27/08/10.

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In 2005, Alzheimer's disease International (ADI) commissioned an international group of experts to review all available data and reach a consensus on dementia prevalence in the 14 World Health Organization regions. The results, published in the ADI Delphi Consensus Study, suggested that the number of people living with dementia would grow from approximately 24.3 million in 2001 to 42.3 million in 2020 and 81.1 million in 2040 (a near doubling every 20 years) (3).

According to the 2001 data from the ADI Delphi study, North America and Western Europe have the highest relative prevalence of dementia, with around 6.4 and 5.4 percent of the population, respectively, compared to a world average of 3.9 percent. However, the overall incidence of dementia shows that the largest concentrations of people with dementia live in the developing world and that most of the growth in the number of people with dementia will come from these countries (2). In Australia the situation is not different; a study made in 2005 by Jorm et. al. found that without prevention, prevalence of dementia is estimated to increase from 172,000 in 2000 to 588,000 in 2050: a 241% increase in 50 years.

However, these numbers could be changed if we could delay the onset of the disease. Jorm, et. al. found that with a delaying of 5 years, the prevalence would decrease by 44%. Furthermore, with 'only' a 6-month delay, the prevalence would decrease by 6% (4).

## Dementia pathology

Pathology helps to differentiate demented and non-demented individuals using thresholds of plaques, neurofibrillary tangles, infarcts, and Lewy bodies. As a result, pathology becomes the "gold standard" for dementia diagnosis (5). AD, the leading cause of dementia in the elderly, is an irreversible, progressive neurodegenerative disorder, clinically characterized by memory loss and cognitive decline. AD is a syndrome for which the definitive diagnosis remains in the neuropathological examination with the demonstration of characteristics of histological changes (6).

In 1997, Braak and Braak identified some age-associated stages in the AD continuum. They stated that "progressions" through Braak stages result in

"regressions" in cognitive function (7). Braak stage I is the point at which tau protein starts to clump into tau tangles. It is apparent that some cognitively normal subjects are in this stage. Stage I is a "preclinical" brain-change state, consistent with a pathological diagnosis of early AD. There are no clinical symptoms at this stage, and it may take up to four decades before there is noticeable dementia.

The pathological process underlying AD can be recognized over extended periods of time before the onset of clinical symptoms. Only a proportion of AD patients live long enough to arrive at end stages V–VI of the Braak spectrum. At stages III–IV, severe destruction of the cortex is already observed; however, it is focused on the entorhinal region and adjoining areas (7).

The onset of dementia seems to pass through a pre-clinical stage in which cognition is borderline compared to normal aging (8). There is considerable evidence that supports the concept of a long prodromal, or pre-clinical, period in the dementia process (9). This period is characterized by the presence of cognitive deficits and neuropathologic alterations that are generally not detectable (10, 11). There is a high likelihood that these individuals eventually would develop MCI and dementia upon longitudinal observation (12).

## Early diagnosis

Early detection and differential diagnosis of dementia are essential for choosing proper therapies aimed at removing the causes of reversible dementias or adequately treating cognitive and behavioral symptoms of progressive dementias (13). Additionally, pharmacological treatment is most effective at improving patient's life expectancy and quality of life when initiated in the early stages of dementia (14). For these reasons, early diagnosis of dementia has become one of the most important areas of clinical focus, with profound implications for establishing the prevalence of dementia, initiating treatment when it may have optimal benefit and understanding the pathobiology of the disease (15).

The process of diagnosing a demented person in the preclinical state is very difficult. When faced with a patient with a potential dementia condition, the clinician must establish a probable diagnosis

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based on evidence available from longitudinal clinical assessment, blood tests, neuropsychological assessment, and structural brain imaging. As a result, there is strong impetus for clinical and epidemiological research to focus on the identification of risk factors that may be modified in pre-dementia syndromes, at a preclinical and early clinical stage of dementia (16).

Pre-mortem differential diagnosis of dementia is typically more reliable in advanced stages of the disease. Importantly, however, accurate clinical diagnosis in the early stages continues to be difficult (17). There is a big necessity to accurately detect the onset of cognitive changes that signal the beginning of a progressive dementia syndrome and to differentiate among disorders with distinct etiologies and sites of pathology. This can be a particularly difficult task given the insidious onset and slow progression of most neurodegenerative diseases, but it is critically important given the lack of a reliable biological marker that can distinguish dementia from normal aging or other neurodegenerative disorders that lead to dementia (18).

The correlation between dementia pathology and its clinical presentation is not fully established. However, Bradley et. al. (19) found that the abnormal brain changes associated with increasing dementia pathology are relevant in terms of intervention. There are at least 30 years between Braak stage I and stage III, and approximately 18 years between stage III and stage V. As a result, dementia develops for many years before symptoms are evident.

The potential treatment for dementia is an area that needs to be studied more, especially now that there is more knowledge in this field. For instance, twin studies indicating insidious changes in cognitive performance may occur up to 20 years before disease onset (20). Therefore, treatment will be most effective at the presymptomatic, earliest stage of the disease before further, irreversible brain damage has occurred (21). The rapidly growing proportion of elderly population, combined with the lack of standard and effective diagnostic procedures that are available to healthcare providers, makes early diagnosis of dementia a major public healthcare focus (14).

## Protective and risk factors in dementia

A recent study by Alzheimer's Australia examined the international evidence for the prevention and risk reduction of dementia (22). This understanding is critical since, while more common as people age, dementia is not a normal part of aging. The study identified factors that may be controlled to reduce cognitive decline and delay or prevent the onset of dementia, as well as those that cannot be modified. It is important to consider that factors that benefit a population will not necessarily have the same effect for every individual.

Protective factors are defined as those that may lower the risk of developing dementia or even delay its onset. The main protective factors identified by Woodward were physical activity, going intellectual stimulation, leisure and social activities, higher education, anti-inflammatory drugs, cholesterol lowering drugs, (7) anti-hypertensive drugs (for those with high blood pressure), and (8) moderate alcohol intake. In addition, control of risk factors may also be considered protective (22).

Scientists have also identified a number of risk factors for dementia. While these are not causes of dementia, they may increase the chances of developing the disease. Additionally, the more dementia risk factors present, the greater the chances of developing dementia. Some of the dementia risk factors include age, genetic factors and family history. Other risk factors include head injury, vascular risk factors (E.g. smoking, diabetes, hypertension, and obesity), fatty diet, low education, depression, and sleep disorders. While many of these risk factors cannot be controlled (E.g. age and genes), important lifestyle changes can be made to reduce the overall risk of developing dementia (22).

## Continuum of aging casualty

According to the combination of protective and risk factors, there are some individuals that will age normally while others will develop dementia at some stage in their lives. It is proposed that the progression towards normal aging or dementia be explained using the concept of "continuum of caretaking casualty"

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introduced by Sameroff and Chandler (23). They proposed that individual differences in caregiving environments contribute to developmental differences across a number of domains. In other words, they explained the transactions between the ecological context and the developing child (24).

Scientific evidence suggests that mental health problems typically develop in a gradual progression, rather than clear stages in which a disorder is absent one moment and present the next (25). Provided this context, it is proposed that neurodegenerative diseases be considered along a similar “continuum of aging casualty” to explain the influence of differences in aging factors (Ej. protective and risk) on the onset and progression of dementia.

The idea of aging casualty implies the importance of the physiological and environmental variables that define the aging process. The expression “continuum of aging casualty” therefore suggests that the interaction between genetic, historical and current environments is crucial in determining the likelihood of developing dementia. There is growing support to the concept that the relationship between normal aging and dementia-related cognitive changes can be expressed in terms of a continuum between normal aging and dementia. It is proposed that individuals that are in the “preclinical” stage of dementia are very sensitive to protective and risk factor modifications. Therefore, the definition of dementia along this continuum further highlights the importance of early detection to provide early intervention and lifestyle changes for those individuals who may be most vulnerable (given the combination of protective and risk factors).

The more vulnerable group is composed of those individuals with diagnosis of mild cognitive impairment (MCI). MCI subjects are those who have an objective and measurable level of cognitive deficit, detectably greater than in normal aging but not including apparent dementia (26). This group falls between people exhibiting cognitive changes of normal aging and those with very early dementia. MCI is often a transitional stage between normal cognitive function and clinical dementia (27). The distinction between normal aging and MCI can be quite subtle and the specific transition between MCI and very early dementia can also be challenging to identify (28).

## **The role of neuropsychological assessment in the early diagnosis of dementia**

Neuropsychological assessment is a fundamental component in the dementia diagnostic process and is considered by many as the best method to identify cognitive impairment (29). However, there is a critical need for effective neuropsychological tools that can identify dementia in its very early or preclinical stages (9). The main objectives of neuropsychological assessment are to: identify early cognitive impairment; make a differential diagnostic; establish the stage of the disease; detect a baseline useful to compare with future assessments and value the evolution and prognosis of the dementia; and assess the efficiency of pharmacological and non-pharmacological treatments.

In the dementia field, the main advantages of neuropsychological assessment are its contribution to determine the: onset of dementia, rate of decline, and response to therapies (30). Accurate neuropsychological assessment is essential in dementia diagnosis because of its value in distinguishing between age-related and disease-related cognitive changes (31).

In the last years there has been great proliferation of assessment tools for dementia that have contributed to advancing diagnosis and treatment of dementia. For example, a brief battery for detecting dementia, including measures of new learning, delayed recall, attention, and executive function, could provide valuable information for screening and diagnosis if interpreted properly (32). However, neuropsychological assessment instruments are not uniform and their results can thus often be confounded by factors that render them somewhat insensitive to measures of cognitive decline characteristic of the early stages of dementia. These factors include wide intra- and inter-subject variability as well as susceptibility to confounding variables such as age, education, language, living situation, fatigue and motivation, and floor and ceiling effects (9, 13).

Another important part of the neuropsychological assessment is the clinical observation. Dementia cannot be diagnosed by neuropsychological tests alone, and clinical judgment is always recommended (32). While the diagnoses are supported by neuropsychological data, the ultimate judgment is that of a

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clinician (33). More specifically, the cognitive markers defined through the neuropsychological assessment process provide valuable information for the clinician to make a diagnosis (34).

### Neurocognitive markers in dementia

In neuropsychological assessment, diagnosis is informed by the identification of markers that relay information about the cognitive state of the person. Neurocognitive markers can help differentiate normal older adults from those with probable cognitive impairment. It is important to promote the identification of clinical markers of those people at risk for developing dementia to assist in detection in its early stages and perhaps even at the preclinical level (35).

Neurocognitive markers that provide information about the preclinical cognitive changes can play an important role in recognizing the first stages of the neurodegenerative process. Complaint may be an early marker of deteriorating cognition, particularly in cognitive domains and testing settings where current normative data are not sufficiently sensitive to capture subtle change. Because cognitive complaint is distressing and can be persistent, there has been recent focus on its potential inclusion in the diagnostic criteria, thus allowing evaluation and treatment of this symptom alone (36).

The functional profile of an individual is defined as the capacity to engage in everyday and social role activities and is evaluated in terms of performance in basic (Ej. eating) and instrumental (Ej. financial planning) activities. Functional decline thus reflects the impairment of the social and occupation functions. It has been used as one of the defining features separating individuals with MCI from those categorized with dementia; specifically, the diagnostic criteria for MCI requires minimal functional impairment (37). However, recent studies suggest that individuals with MCI display functional changes that are not present in healthy older adults. These studies have found that instrumental abilities are prone to be affected earlier in the continuum (Ej. during the preclinical stage) and prior to fulfillment of the diagnostic criteria for dementia.

Instrumental activities of daily living (IADLs) have been described as a complex range of activities

that facilitate independent living, including such varied things as financial management, food preparation, telephone use, medication management, driving or travelling, housekeeping and shopping. The ability to deal with finances, meal preparation, housekeeping, and shopping have been identified as the earliest IADLs to deteriorate, suggesting increased vulnerability to cognitive decline (37). Therefore, functional decline is a potentially valuable neurocognitive marker.

Behavioral measures linked closely to early neural changes may promote our understanding of MCI transitions and our ability to detect incident cases at the earliest possible point, ultimately assisting in the early detection of dementia (26). For example, speed of processing can be measured using the rate at which a task is performed as a standard level of performance or first indicator (38). Speed may thus be a sensitive neurocognitive marker for a variety of higher order cognitive abilities in both normal cognitive decline (even in very late life) and during the early emergence of cognitive impairment (26). Consequently, a decline in speed (and potentially other behavioral measures) may be linked to a corresponding decline in overall functional abilities and can be used as a marker of early detection.

Verbal memory deterioration may represent another key neurocognitive marker for distinguishing normal subjects from demented patients (34). At the onset, episodic memory impairment represents one of the main features of dementia (8). More specifically, verbal episodic memory is one of the first domains of cognition to be affected in the dementia process (9). In the preclinical dementia state, studies indicate that the greatest deficit occurs in episodic memory (11). More specifically, Flower et. al. identified that paired associate learning and delayed matching to sample are very sensitive to early dementia (39, 40).

### CONCLUSIONS

Scientific evidence highlights the importance of recognizing individuals in the preclinical stage (Braak stage I) of the dementia continuum to prevent or delay the onset of symptoms. A yet unanswered question is why some patients do not present cognitive impairment, despite the fact that the presence

of the disease pathology increases the risk of developing dementia symptoms.

The concept of “continuum of aging casualty” is proposed as a way to view the progression of dementia as dependent on a combination of risk and protective factors. More specifically, the interaction between genetic, historical and current environments is crucial in determining the likelihood of developing dementia, especially in the MCI group. Even though there is no specific treatment for MCI, the concept of “continuum of aging casualty” suggests that it may be possible to prevent the appearance of the disease symptoms through the implementation of strategies (such as lifestyle changes) that reduce risk factors and increase protective factors.

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