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Mild Cognitive Impairment – History, Diagnosis and Treatment

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ABSTRACT

Over the last twenty years, mild cognitive impairment (MCI) has come to the forefront of research because of the conversion rate of 10-15% annually to dementia, usually Alzheimer type, and with 40% conversion within 3-4 years. The need exists to treat dementia, especially Alzheimer's type, early on which may delay the progression of conversion and providing financial savings on a societal macro-level but also individual micro-level. Accordingly the diagnosis of MCI as the pre-dementia state is of the utmost importance. However not all MCI cases will convert, so there exists the prerequisite of finding the predictors for detecting the converters. The direction of research varies from neuroimaging, biochemical markers in blood and/or CSF, or clinical neuropsychological markers.

This article will provide the history of defining the concept of MCI and an approach to the diagnosis, treatment, both pharmacological and non-pharmacological.

Keywords

Mild Cognitive Impairment; MCI definition, MCI diagnosis, MCI treatment.

Introduction

With the increase in the absolute number of elderly over 65 from around 700 million presently to 1.9 billion by 2050, there will be an accompanying increase in the number of persons suffering from some form of cognitive decline, which as a result will become a major factor in health care for the present millennium. At present, the prevalence of dementia is estimated to be around 10% at 65 but increases four-fold to 40% by the age of 85 years [1]. In the world today, around 35 million persons have been diagnosed with dementia and with incidence rate of 4.6 million new cases every year, the numbers will eventually increase to 106 million by the year 2050 [2]. As a consequence, society has found their limited resources strained, with inadequate funding and too few places in institutions for the demented elderly. Accordingly if one is able to delay the cognitive decline by even a few months to a year, then the financial savings, both on a national and a personal level, will be significant [3].

Once a person has been diagnosed as suffering from dementia, irrespective of type, the efficacy of treatment tends to decrease with the progression of the disease. Starting treatment in the early stages has resulted in a decrease in care-giver burden and may even delay institutionalization by up to a year [4]. Therefore, there exists a need to diagnose the disease as early as possible. Accordingly, research is now directed towards diagnosing these early stages of cognitive impairment in an attempt to predict those who will proceed to develop dementia. Studies have shown that the early stage of cognitive decline, termed mild cognitive impairment (MCI), has a prevalence of 15-20% in the population aged 60 and older [5] and has a variable conversion rate to dementia of 10-12% per year [1] but even higher rates have been reported in those visiting specialized memory clinics [6].

Since cognitive decline develops over an extended period of time, the importance of defining and identifying MCI has become even more relevant in the face of new treatment modalities on the market and the necessity to start these treatments in the early stages of the disease [7]. It is now known that on pathological examination of autopsy tissue, MCI was shown to be an intermediate stage between the changes of normal aging and the pathological features of very early dementia with neurofibrillary pathology in entorhinal cortex, hippocampus and amygdala [8].

Accordingly, this article will attempt to describe the historical

development of the concept of MCI and to give a review of the entity relating to the constructs for the diagnosis, its prevalence and relevance and different treatment approaches both, pharmacological and non-pharmacological for the entity.

Mild Cognitive Impairment – its historical development

As mentioned above, cognitive decline develops over an extended period of time [9] during which the patient passes through various stages, often classified by global scales such as Morris's Clinical Dementia Rating (CDR) scale [10] and Reisberg's Global Deterioration Scale. There exists therefore an interim stage where the screening instruments for detection of cognitive decline are normal yet there is actually some memory impairment. It is important to remember that the global scales are not accurate enough for defining the clinical state of cognitive decline [11] but are useful as guidelines.

The concept of early onset of a dementing process is not a new one. Kral back in the middle of the last century reported on the problem and termed the process Benign Senescent Forgetfulness [12]. Over the years it has been called different names by different authors (Table 1). In 1982, Reisberg and colleagues termed the problem Mild Cognitive Dysfunction, and this was defined as having at least two of the following: getting lost in unfamiliar surroundings, decline in work performance, apparent deficits in word naming, loss of retention of new material, or deficit in concentration [13]. Later Crook and his fellow researchers coined the term Age Associated Memory Impairment (AAMI) and attempted to define more specifically that the person be over the age of 50 years, score 1 Standard Deviation (SD) below the young in memory tests, and have a subjective complaint of memory loss, but with normal intellect function and no diseases affecting memory [14]. Levy (together with Working Party of International Psychogeriatric Association) [15] felt that there was a need for an even more structured definition of memory disturbance by use of neuropsychological tests, graded by age and education, and decided to rename the entity as Age Associated Cognitive Decline (AACD).

Terminology	Year/ Author	Constructs
Benign Senescent Forgetfulness (BSF)	1958 V.A. Krall	Preceded by concepts of "normal senility", "normal senescent decline". Regarded as variant of normal aging memory changes with inability to recall data.
Limited cognitive disturbance (LCD)	1982 B.J. Gurland	Decline in memory, increased reliance on notes, forgets names/dates/misplaces things, dangerous memory lapses, errors on cognitive testing
Mild cognitive decline (MCD)	1982 B. Reisberg	Getting lost, Decline in work performance, Deficits in word naming, loss of retention of new material, deficit in concentration.
Questionable Dementia (QD)	1982 C. Hughes	Objective evidence of cognitive impairment, Affects social and occupational function, 2SD below mean on memory tests. Regarded as worse end of MCI
Age-Associated Memory Impairment (AAMI)	1986 T. Crook	Age over 50, subjective memory loss, below 1SD on memory tests, adequate intellectual function, Absence of dementia
Minimal dementia	1986 M.E. Roth	Cognitive deficits in memory and minor errors in orientation. No evidence of impairment in function
Age-Consistent Memory Impairment (ACMI)	1989 R.C. Blackford	Between 50-79, Subjective memory loss, Performance within 1SD of aged norms on 75% of tests, Preserved intellect.
Late Life Forgetfulness	1989 R.C. Blackford	Impaired memory performance (1-2 SD below mean of aged norms) on 50% of memory tests.
Mild Cognitive Disorder (MCD)	1992 H. Christensen	Decline in cognitive performance including memory, learning or concentration. May precede, accompany or follow physical disorder.
Age-Associated Cognitive Decline (AACD)	1994 R. Levy	Self or informant report of memory loss, Gradual onset over 6 months, Objective difficulties in any of following: learning and memory, attention and concentration, thinking, language and visuospatial function.
Mild Cognitive Impairment (MCI)	1994	See text.
Cognitive Impairment Not Demented (CIND)	1995 E.M. Elby	Cognitive impairment in one or more domains but no dementia by DSM-IV criteria,
Subclinical Senescent Cognitive Disorder	1996 K. Ritchie	Commonly perceived as a normal feature of normal aging process. Heterogeneous entity.

Table 1: Synonyms for Mild Cognitive Impairment (MCI).

Later, Petersen and his colleagues decided to adopt the term Mild Cognitive Impairment (MCI) to explain this clinical phenomenon [16] and defined it as a complaint of memory loss by the patient himself, his family or his physician; with normal performance of activities of daily living and normal global cognitive function, but with an objective memory loss greater than 1.5 SD on neuropsychological testing while controlling for age and education. According to Petersen's definition, it was important to ensure that there was no dementia present, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association, and that the person was between the ages of 60 and 89 years. However with the use of revised diagnostic criteria, as defined by an expert group in Stockholm in 2003 [17], there was significant improvement in the diagnosis of MCI with the inclusion of a criterion relating to increasing difficulty in performance of everyday tasks without loss of autonomy [18].

There is still much debate as to the naming of this clinical entity with some authors calling it Cognitive Impairment Not Demented (CIND), Limited Cognitive Disturbance (LCD), Questionable Dementia (QD), Minimal Dementia, Age-Consistent Memory Impairment (ACMI), Late Life Forgetfulness, Subclinical Senescent Cognitive Disorder and others. Some of these terms with their main features are described in table 1. However, most clinicians and researchers use the preferred term MCI. There

have been proposed four clinical subtypes of MCI: amnestic-MCI, which is subdivided into either single (only in memory) or multiple domains, and nonamnestic-MCI, which similarly is subdivided into either single domain or multiple domains (Figure 1). The importance of the subdivision is that it has been claimed that amnestic MCI, single domain or multiple domain, is a precursor to the development of Alzheimer's Disease whereas the multiple domain non-amnestic MCI is more likely to progress to Vascular Dementia or Dementia of Lewy Body and the single non-amnestic MCI is preclinical entity for Frontotemporal Dementia or Dementia of Lewy Body [11,19].

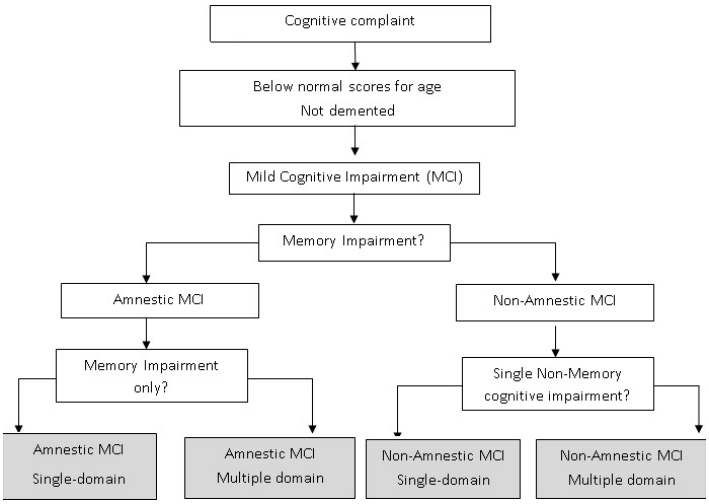

Figure 1: Flow Chart of amnestic and non-amnestic MCI.

Since the pathology in the brain often develops up to 20 years before the clinical diagnosis of MCI, the trend lately is to try and diagnosis pre-MCI stage termed subjective cognitive impairment (SCI) [20] which may offer the answer to an even early treatment of cognitive impairment.

Diagnosing MCI

The means to diagnose MCI are varied and somewhat dictated by the resources available to clinicians. Researchers have focused on the use of clinical markers, neuroimaging, CSF and genetic biomarkers for the diagnosis of MCI [21].

Research has shown neuroimaging to be useful, especially with regard to hippocampal and medial temporal lobe atrophy [22-24] which are consistent with the loss of neuronal cells described by histopathology studies. Neuroimaging documents either the structural anatomical changes by means of computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) using a tracer for beta-amyloid plaques using Pitssburgh Compound–B (PIB), or functional physiological changes by single-photon emission computed tomography (SPECT) perfusion imaging or PET scan imaging of glucose metabolism in the medial temporal lobe using 2-[18 fluoro-2-Deoxy-D-glucose (FDG) [24,25]. Mueller and colleagues reported on neuroimaging studies with high-resolution T2 weighted MRI for imaging sequence to hippocampus and were able to manually mark the entorhinal cortex, and the subfields of the hippocampus of subiculum, CA1 (important for temporal information and most affected by Alzheimer's Disease), CA1-CA2 transition zone, CA3 (important for spatial information) and dentate gyrus. It was shown that the patterns of neuroimaging were consistent with patterns of neuronal loss/reduced synaptic density found in histopathology of persons with dementia (in the area of CA1) and MCI (in the area of C1-CA2 transition zone).

Another approach used by researchers has been the use of biomarkers, particularly in the cerebrospinal fluid (CSF), to define those who will develop dementia [26]. Studies have found that the levels of beta-amloid 1-42, total tau protein (t-tau) and phosphorylated tau (p-tau181P) in the CSF fluid had good accuracy for impending dementia in MCI and in fact it is claimed that the combination of these markers with MRI structural changes provided better prediction for development of dementia [27]. Low CSF beta-amyloid1-42 has been show to be a marker of fibrillary amyloid deposition in plaques, whereas increased CSF t-tau and CSF p-tau181p are markers of neuronal injury which correlate with stage and load of neurofibrillar tangles. However, the use of biomarkers in CSF is mainly research based and clinically may be useful in atypical cases such as persons younger than 55 or persons with rapidly progressive dementia and in cases to exclude other causes of cognitive decline such as infection in the central nervous system, hydrocephalus, autoimmune diseases or cancer.

Research has also related to the genetic testing [28]. Reports on apolipoprotein E alleles (ApoE) have shown that ApoE4 indicates an increased vulnerability especially to Alzheimer's Dementia where as ApoE2 indicates relative protection. The problem is that the test is very expensive and by no means a diagnostic test and often raises more questions than answers. Other genetic markers such as chromosome 14, presenilin-1; chromosome 1, presenilin-2; chromosome 21, APP are in the process of being studied. These seem to be responsible for most cases of familial early-onset, autosomal-dominant AD (with onset before the age 65 years) and these forms are responsible for less than 1-2% of cases [29].

However, most clinicians have limited resources for neuroimaging, biomarkers or genetic testing and tend therefore to rely on clinical and neuropsychological markers to help them in their decision making [1]. Commonly used screening instruments for assessment of general cognitive dysfunction, such as Folstein's Mini-Mental Status Examination (MMSE), are usually normal, so the diagnosis of MCI relies on the results of neuropsychological tests done either by means of pen and paper or by computer programs [30]. The instruments used for clinical assessment need to examine episodic memory (the ability to learn and retain new information) for both immediate and delayed recall. The neuropsychological battery of tests may comprise a number of different individual instruments for testing episodic memory such as Rey's Auditory Verbal Learning Task (RAVLT), California Verbal Learning Test (CVLT), or delayed recall of a paragraph from the Wechsler Logical Memory Scale. However there is a need also to examine areas such as executive function (by means of instruments such as Trial Making Test A/B), language (using letter and category fluency), visuospatial skills

(using figure copying), and attention control (by means digit span forward and backward) [31]. Some clinicians may use more battery of tests, such as the Neurobehavioral Cognitive Status Examination (COGNISTAT®), Montreal Cognitive Assessment (MoCa), St. Louis Mental Status (SLUMS) examination or others. Of course the test results for the instruments have to be corrected for age and education level; nonetheless abnormal results on these more sensitive instruments are more definitive for memory problems. In the article by Trezepez [32], it was shown that the MoCA was a more sensitive instrument for the detection of MCI using the cutoff point of 18/30. The sensitivity of MoCA to diagnosis MCI was reported to be between 80-100% but the price for ruling-in the diagnosis is a lower specificity (50-70%) [33].

An attempt to define MCI clinically was done by the Alzheimer's Disease Cooperative Study Group for the multicenter Memory Impairment Study [34] and the operational criteria were established using only a simple memory test of paragraph recall, measure of general cognition using the MMSE, and a structured clinical interview for global clinical impression by CDR.

Prevalence and relevance of MCI

The prevalence rate of MCI has a variable range from 3-20% and largely is a function of definition and operational criteria [35] but the mean time for conversion from MCI to dementia has been reported to be about 2 years [36]. A review by Luck and colleagues [37] noted that overall, incidence rates of 51 to 76.8 per 1,000 person-years for developing MCI. The authors noted that higher age, lower education and hypertension were high risk factors. They concluded that there is need for agreement concerning the criteria used for defining MCI and the operationalization of these criteria.

The need for diagnosing MCI and predicting which persons will develop dementia in the future becomes apparent when one realizes that many of those with MCI will develop full-blown dementia [1,21,38-40]. The conversion rates have been reported from 12% per annum [5] to 100% over 9.5 years [10], indicating the difficulty in the definition of the entity MCI. The difference in conversion rates does not necessarily mean that there are different disease processes but rather that different studies captured different stages of disease severity within their study population [6]. It is claimed rather that the conversion rate is largely dependent on the degree of functional impairment at baseline rather than dependent on the actual recruitment site (community or clinic) [36]. It has been argued that no single risk factor appears sufficient for accurately prediction conversion but rather a complex panel of entities such as age, neuropsychological test results, functional status, ApoE, neuroimaging, CSF biomarkers and vascular risk factors may be required akin to the predictors of cardiovascular disease [40].

Treatment of MCI – Pharmacological and non-pharmacological

Before any trial of therapy, pharmacological or non-pharmacological, is initiated, persons with MCI should be assessed for reversible causes of cognitive decline such as thyroid disease, vitamin B12 deficiency and other cause. In addition concomitant medication use should be assessed for potential risk and side effects. In a study by Weston and colleagues [41], it was reported that using 2003 Beers Criteria for inappropriate medication, 20.8% of persons with MCI were taking some sort of inappropriate medication especially anti-cholinergics, benzodiazepines and/or sedatives.

A major problem in relating to the efficacy of treatment in MCI was that the trials had differing conversion rates and may be related what was stated above that different criteria were used for defining MCI. The literature reports a positive effect of treating those with a dementing process at its earliest stages [3], so the trend now is to initiate trials to test the use of treatment with cholinesterase inhibitors or memantine in those with MCI [5], but the variables predicting future cognitive decline are in a state of uncertainty.

Trials have been reported with varying outcomes with the use of cholinesterase inhibitors such as donepezil in the Alzheimer's Disease Cooperation Study (ADCS) group [40], rivastigmine in the Novartis trial, galantamine in the Johnson & Johnson trial and mostly have not shown convincing effects in delaying progression from MCI to dementia [6,21]. The debate with the regard to use of memantine still exists with differing approaches. However any trial of therapy requires a longitudinal study of many years and at this stage is not feasible. However as reported in a study by Weistein and fellow researchers in California, USA , almost a fifth of MCI patients were being treated with "off-label" cholinesterase and memantine medication [42].

There has been a re-emergence in recommendation of use of the purified extract of gingko biloba (Egb). It has been shown to improve cognition, decrease behavioral problems increasing the quality of life and most important with less side effects [43,44].

Recent focus has shifted to non-pharmacological interventions such as management of risk factors such as diet, changes in lifestyle and cognitive intervention programs [33]. Use of nutritional supplements such as Chinese herbal remedies or vitamins has been shown to also have some possible beneficial effects [45]. In the ACTIVE study (Advanced Cognitive Training for Independent and Vital Elderly), it was shown that 5 years after cognitive training, some improvement in memory, reasoning and speed of processing was still maintained [46]. Sherman and colleagues [47] reported in their review of the literature that cognitive intervention based on multicomponent training or multi-domain strategies may actually increase hippocampal activity. These positive findings improved cognition, working memory, language, and executive function. Though improvement has been shown in ADL functioning, mood and memory, no evidence showed delay in progression to dementia [21]. What is important to remember that participants in the cognitive training program reported satisfaction with the course and felt improvement in some areas of the memory [48].

Summary

The entity of Mild Cognitive Impairment includes a person's self-awareness of loss of memory, metamemory disturbance, and this is

usually the driving force behind the decision to turn to a physician for advice. MCI is a common disorder amongst the elderly and has a variable prevalence in the elderly and is accepted as defining a transitional state between the cognition decline of normal aging and mild dementia. The importance of diagnosing MCI is that people experiencing MCI have a greater risk for conversion to dementia at a later stage.

The need exists for examining predictors of future dementia in those with MCI when one realizes that within a few years, over half of those with MCI will develop full-blown dementia. The trend now is to start treatment, pharmacological and/or non-pharmacological, as early as possible even at this stage of MCI, since the early treatment is started the more effective it is in slowing the progression of the disease.

Many medical conditions may predispose to another medical condition for example hypertension for stroke and heart disease and the predisposing medical condition often has a prodromal phase which if treated early may prevent further deterioration. In this way, MCI should be viewed as a clinical syndrome that has a high risk of progressing to dementia. Thus if clinicians were to consider MCI not as incipient dementia but as a risk factor for developing dementia, certain issues concerning management and treatment for dementia may also be relevant also to MCI. It could be stated that MCI is not a disease or a disorder but a risk factor for developing dementia.

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