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Mild Cognitive Impairment: A Systematic Review

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Abstract. MCI is a nosological entity proposed as an intermediate state between normal aging and dementia. The syndrome can be divided into two broad subtypes: amnestic MCI (aMCI) characterized by reduced memory, and non-amnestic MCI (naMCI) in which other cognitive functions rather than memory are mostly impaired. aMCI seems to represent an early stage of AD, while the outcomes of the naMCI subtypes appear more heterogeneous -including vascular dementia, frontotemporal dementia or dementia with Lewy bodies- but this aspect is still under debate. MCI in fact represents a condition with multiple sources of heterogeneity, including clinical presentation, etiology, and prognosis. To improve classification and prognosis, there is a need for more sensitive instruments specifically developed for MCI as well as for more reliable methods to determine its progression or improvement. Current clinical criteria for MCI should be updated to include restriction in complex ADL; also the diagnostic and prognostic role of behavioral symptoms and motor dysfunctions should be better defined. A multidisciplinary diagnostic approach including biological and neuroimaging techniques may probably represent the best option to predict the conversion from MCI to dementia. In this review we discuss the most recent aspects related to the epidemiological, clinical, neuropathological, neuroimaging, biochemical and therapeutic aspects of MCI, with specific attention to possible markers of conversion to dementia.

Keywords: Alzheimer disease, apolipoprotein E, biomarkers, diagnosis, mild congnitive impairment

INTRODUCTION

Over the last decade a great amount of scientific effort has focused on the gray area between cognitively normal aging and dementia in order to define what can still be considered normal at different ages and what, on the other hand, is already the prodromal phase of an clinically disclosed dementia. The concept of "cognitive impairment not yet dementia" has been depicted by different definitions with variable prognosis (Table 1). Among them, Mild Cognitive Impairment (MCI) has become the term most frequently used and defined by slight impairment in cognitive functions with otherwise normal function in the activities of daily living [103].

The original criteria of MCI were related to an amnestic form, lately defined as aMCI, characterized by the presence of isolated memory impairment, memory complaint, relatively intact activities of daily living, normal general cognitive function and absence of dementia [99]. Using this definition in population studies, it was shown that aMCI constituted only a relatively small group, compared with all individuals with a much broader form of mild cognitive deficits in other cognitive functions such as language, attention, visuospatial skills, and executive functioning [46,65,70, 111]. Thus, Petersen [103] revised the original criteria and four different MCI subtypes have been proposed: (1) the former aMCI; (2) single non memory MCI (snmMCI), with isolated impairment of a cognitive domain other than memory; (3) multiple domain amnes-

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Table 1
Clinical terms proposed to define cognitive impairment not yet dementia

Term	Initial description	Diagnostic criteria
Age-associated memory impairment	Crook and co-workers [28]	Subjective memory impairment with objective memory impairment compared with that of a young adult
Late-life forgetfulness	Blackford, LaRue [19]	Age-associated memory impairment plus age-adjusted deficits in four or more specific cognitive tests
Mild cognitive decline	ICD-10 [128]	Impairments in cognitive tests of learning, memory, or concentration secondary to defined illness
Questionable dementia	Morris [91]	Scoring 0.5 at Clinical Dementia Rating scale
Aging-associated cognitive decline	Levy [67]	Age-adjusted impairment on any cognitive task
Mild neurocognitive decline	DSM IV [2]	Impairments in memory, learning, perceptual-motor, linguistic, or executive functioning
Cognitive impairment–no dementia	Graham and co-workers [51]	Impairments in memory, learning, perceptual-motor, linguistic or executive functioning in the absence of clinically defined dementia
Mild Cognitive dysfunction	Johansson and Zarit [59]	Dysfunction according to five cognitive tests
MCI	Petersen and co-workers [99]	Subjective complaint of memory impairment with objective memory impairment adjusted for age and education in the absence of dementia. The definition was then expanded to include four clinical MCI subtype
Subclinical cognitive impairment	Ritchie and co-workers [112]	Scoring below a specific scor on the Dètèrioration Cognitive Observèe, a test sensitive to early change in cognitive functioning
Cognitive impairment, no dementia	De Ronchi and co-workers [34]	Scoring 2 or more S.D. below the mean score of MMSE, corrected for age and education, calculated among the non-demented people

Modified from De Carli [32].

tic MCI (mdMCI^{+}), characterized by a slight impairment of multiple cognitive domains including memory; (4) multiple domains non amnestic MCI (mdMCI^{-}), with a slight impairment of multiple cognitive domains but without memory deficits. However, there is still a lack of consensus on what types of cognitive tests, how many, and what thresholds or cut-off should be used to support or corroborate the diagnosis of MCI [72].

Longitudinal studies suggested that MCI represents a condition at high risk of progression to dementia, but rates of conversion vary among studies. Progression to dementia generally appears to be higher in clinic-based studies with a yearly incidence of about 10–15%. Instead, population-based studies report lower rates, ranging from 5 to 10% per year [32,95]. Moreover, in population-based studies, a significant rate of reversion (20–25%) from mild cognitive impairment to normal cognition and functioning was observed [94,111]. The discrepancy of progression rates to dementia between clinic- vs population-based studies probably reflects differences in population characteristics, length of follow-up and definition of cognitive impairment. Furthermore, the possibility of selection bias should be taken into account when examining data from clinic-based study.

According to the proposed four clinical subtypes of MCI, it is conceivable that they differ in etiology and outcome. In fact, aMCI and mdMCI^{+} are considered to have a high likelihood of progression to Alzheimer's disease (AD), while snmMCI and mdMCI^{-} are assumed to convert more frequently to non-AD dementia [12,98,103]. This aspect was recently confirmed by a German longitudinal study showing that, at six-year follow-up, subjects with mdMCI^{-} were more likely to progress to a non-AD dementia, and those with mdMCI^{+} converted mostly to AD [21]. Conversely, data from an Austrian community birth cohort study found that, after thirty months of follow-up, the aMCI subtype evolved towards both AD and non-AD dementia and many patients developed AD from non amnestic MCI [42]. According to these as well as to previous data [65,89,104,111], MCI appears to be an extremely heterogeneous clinical entity in terms of etiology, clinical presentation and outcome and much effort is needed for developing a more uniform diagnostic classification and better defined operational criteria.

EPIDEMIOLOGY

Prevalence and Incidence of MCI

Population-based studies in older adults (age $\geqslant$60 or $\geqslant$65 years) performed in North America and Europe reported a prevalence of MCI ranging from 11% to 17% [35,46,51,70,111], higher than previously reported prevalence of dementia (6–8%) [35,51,70].

Prevalence of the aMCI subtype was estimated between 3 and 5% [70,76]. Likewise, in the Canadian Study of Health and Aging, the prevalence of "circum-

scribed memory loss" or "isolated memory deficit", a clinical construct similar to aMCI, was about 5% [43]. Very few studies addressed this aspect in the oldest old population [104].

Regarding the incidence rates, the few studies published to date considered only the aMCI subtype, with a range from 9.9 to 21.5 per 1000 person per year in people older than 65 years [65,120].

Most of the variability in prevalence and incidence estimates of MCI is probably due to the different operational criteria used rather than to the characteristics of the studied populations.

Risk Factors for MCI

Not many studies have prospectively addressed the role of putative risk factors for MCI. Three short-term longitudinal studies, carried out in subjects with MCI, identified as risk factors older age, low education, being African American, presence of apolipoprotein E ε4 allele (ApoE 4), cortical atrophy at neuroimaging, signs or symptoms of vascular diseases and depression [14,71,123]. In a recent three-year prospective study, the authors found that a previous diagnosis of psychosis, hip fracture and polypharmacy increased the risk of cognitive impairment in non demented subjects, independent of subsequent development of dementia [89]. Furthermore, three long-term prospective studies described midlife alcohol drinking, elevated serum cholesterol, high diastolic blood pressure, ApoE ε4, and white matter hyperintensities as risk factors for MCI in late life [8,31,63].

Prevalence of vascular risk factors in different MCI subtypes was evaluated in more than two hundred subjects with MCI collected in the ReGAl project (Rete Geriatrica Alzheimer – Geriatric Network on Alzheimer's disease), the largest longitudinal Italian multicentric clinical-based study on aging and dementia, promoted by the Italian Society of Gerontology and Geriatrics (SIGG). This project, initiated in 2001 and still ongoing, involves 35 Geriatric Memory Clinics all over Italy and is coordinated by the Institute of Gerontology and Geriatrics of the University of Perugia. Methods of the ReGA1 project have been described in more detail elsewhere [106]. From the analysis of collected data, a different vascular risk profile among different MCI subtypes was found, with subjects with snmMCI having a higher prevalence of ischemic heart disease and of TIA/stroke, a higher Hachinski ischemic score, and a higher prevalence of white matter lesions on CT/MRI scan compared to aMCI (submitted paper). These data suggest that, as with dementia, the heterogeneity of clinical expression in different MCI subtypes is probably related to a different pathogenesis, that may include both degenerative and vascular factors.

Mortality

There is little information on mortality rate in MCI and in the different MCI subtypes. A prospective community study of the Mayo Clinic Group demonstrated an increased mortality in subjects with aMCI compared to normal control subjects over a six-year follow-up. Mortality was greater in mdMCI than in aMCI [56]. A recent review reported a non significant increase in mortality for subjects with MCI compared to cognitively intact subjects [51]. However, only few studies are available on this issue, and a comparison of the literature is problematic, due to variations in criteria and methodology.

COGNITIVE STATUS

Currently, the diagnosis of MCI is mainly based on results at neuropsychological tests. The large variability due to measurement errors, lack of appropriate normative data and difference in sensitivity and specificity of the neuropsychological batteries more commonly used, can cause misclassification. In the original MCI criteria, Petersen and collaborators [99] suggested a cut-off of at least 1.5 standard deviations below the age- and education-adjusted values for defining as "mild" the impairment in different cognitive domains. Among cognitive tasks, neuropsychological tests assessing delayed recall, executive functions and selective attention have been found to better predict the conversion of MCI to dementia [3,27,122], but with a sensitivity and specificity usually lower than 70% [88]. Conversely, it was recently shown that the performance at the CERAD-10-word list (CERAD-CWL), a task evaluating long-term verbal recall, was highly sensitive for detecting MCI [118]. Using correspondent analysis to derive a weighted score for each subject from their item responses over the three immediate- and one delayed-recall trials of the CERAD-CWL, the authors found that comparing MCI versus normal subjects, accuracy was 97%, sensitivity 94% and specificity 89%. For MCI/mild dementia versus normal subjects, accuracy was 98%, sensitivity 96% and specificity 91%.

Specific cognitive batteries for MCI have not been proposed yet, although there is a need for sensitive, user-friendly, MCI cognitive screening tests for clinicians. Recently, the Montreal Cognitive Assessment (MOCA) has been developed [93]. This test represents a brief cognitive screening tool with high sensitivity and specificity for detecting MCI, as currently conceptualized, in patients performing in the normal range on the Mini-Mental State Examination. With the same purpose, Li and collaborators [68] showed that using a brief instrument combining a single-item informant report of the memory problem and a four-item Instrumental Activities of Daily Living (IADL) scale, it is possible to differentiate MCI and mild AD from normal aging with high accuracy, sensitivity and specificity.

FUNCTIONAL STATUS

The original criteria for MCI provided for intact activities of daily living (ADL), but the current recommendations indicate that basic ADL (BADL) should be mainly preserved, and that a "minimal impairment" in instrumental ADL (IADL) may be accepted [129]. However, to date non specific instruments for evaluating complex activities of daily living in MCI have been proposed, and there is a need for a consensus regarding the degree of functional decline that can be considered acceptable in the frame of MCI definition [49]. Analyzing the functional characteristics of subjects with MCI collected in the ReGAl study, it was found that subjects with MCI had a more severe IADL disability than cognitively healthy elderly controls, particularly in shopping, self-administration of drugs, and in handling economy. These IADL disabilities were significantly associated with the degree of cognitive impairment, but not with the somatic comorbidity [40]. Consistent with these findings, Bennett and collaborators [18], in their study population of MCI, did not detect impairment in BADL while the IADL impairment was highly prevalent, with 53% of subjects needing help with housework and 43% with shopping. Similarly, in another study, it was found that MCI patients have limitations in everyday tasks that involve either memory (i.e. finding things at home, keeping appointments, and remembering information from a conversation or from television) or complex reasoning (i.e., checking the bank account, shopping, organizing travel), whereas they have normal abilities on basic ADL [97].

Furthermore, recent data suggest that the inclusion of IADL restriction in MCI criteria improves the prediction of a subsequent dementia as well as the stability of MCI condition over time [96]. Incorporating difficulties in performing the activities of daily living with the alterations in non-memory cognitive functions has been found to ameliorate the original diagnostic algorithm for MCI and better detect subjects at risk of convertion to dementia [11].

NEUROPSYCHIATRIC SYMPTOMS

Neuropsychiatric symptoms (NPS) have not been included in the diagnostic criteria and only recently some studies described the neuropsychiatric features of MCI [24,39,44,48,57,73]. According to these studies, frequency of NPS in MCI ranges from 35% to 59%, substantially mimicking the neuropsychiatric involvement of AD. In particular, anxiety-depressive symptoms, apathy, irritability and agitation appear to be the most common NPS in both conditions [39,73,74]. A similar spectrum of affective disorders was observed in subjects with MCI in the ReGAl project: depression and anxiety were, in fact, the most common symptoms, observed in about 33% of subjects, followed by apathy (22%) and irritability (20%). Their presence was associated with a more severe somatic comorbidity and functional disability, both in ADL and IADL [77].

Among affective disorders, depression has been described as a predictor for a subsequent cognitive decline [15,131] and as an independent risk factor for the development of MCI [14]. Depression predicted a faster cognitive deterioration in subjects with aMCI, increasing the risk of conversion to dementia [87].

Recent data showed that a previous diagnosis of psychosis independently increases the risk of MCI [89]; furthermore MCI subjects who convert to AD have a higher frequency of apathy compared to non-converters [113].

NEUROPATHOLOGY

Relatively few data on the neuropathological features of MCI are present in the literature. Results from the Religious Order Study showed that more than one half of persons with MCI met the National Institute on Aging-Reagan criteria for AD. However, about one third of them had also cerebral infarctions [17]. Similarly, in a recent study describing the neuropathological features of aMCI the authors found that many patients did not fulfil the neuropathologic criteria for AD

but their pathologic findings showed characteristics of a transitional state of evolving AD. Although medial temporal lobe structures, as typical of subjects with AD, were involved in all aMCI, they had also other concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions [100]. Presence of neurofibrillary tangles rather than amyloid deposition seems to be more preminent in MCI compared to cognitively healthy controls, with the highest values in early AD. The numbers of neurofibrillary tangles in entorhinal cortex and hippocampus are related to the progressive memory loss. This suggests a continuum of neurofibrillary tangle pathologies underlying transition between normal aging, MCI and early AD [79].

NEUROIMAGING

Several neuroimaging studies described the structural and functional changes of subjects with MCI. The most consistent data derived from structural magnetic resonance imaging (MRI). Subjects with MCI show atrophy of the entorhinal and hippocampo-amygdala regions with an intermediate degree between that observed in normal aging and in AD [116]. Rusinek et al. [115] reported that the medial temporal lobe atrophy rate was the most significant predictor of conversion from normal aging to MCI, with 91% specificity and 85% sensitivity. In addition to hippocampal atrophy, alteration of parahippocampal white matter fibers has been suggested as contributing to memory decline in elderly individuals with MCI by partially disconnecting the hippocampus from incoming sensory information [121]. Concerning specific MCI subtypes, recent data show that mdMCI and aMCI have distinct brain structural abnormalities. While both groups have mesial temporal and cortical volume loss, those with aMCI have a more severe involvement of the mesial temporal structures and less of the neocortical heteromodal association cortices than mdMCI [16]. However, quantification of brain volumes has not been standardized for clinical use, and volumetric MRI is not currently included in the diagnostic work-up of MCI.

Compared to MRI, a small number of functional imaging studies have been conducted in MCI. Data obtained using [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) showed that the reduction in glucose metabolism in the hippocampus significantly improved diagnostic accuracy for MCI over MRI hippocampal volumetric measures (85% versus 73%) [30].

There have been increasing efforts to develop diagnostic neuroimaging methods able to detect amyloid or tau proteins. Radiolabelled PET tracers, which bind to amyloid plaques and neurofibrillary tangles in vitro, have been a matter of intense investigation. A recent study conducted with 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile (FDDNP) PET showed that the global FDDNP binding (average of the values for temporal, parietal, posterior cingulated, and frontal regions) in MCI subjects was significantly higher than in controls and lower than in AD. These data suggest that FDDNP-PET is able to differentiate MCI from controls and AD, probably more accurately than FDG-PET or volumetric MRI measures [119].

Another recent technique previously used in AD and then applied to MCI, is proton magnetic resonance spectroscopy (^{1}H-MRS), a useful tool for the in vivo assessment of several biochemical compounds of the brain. Data from Catani and collaborators [23], showed that subjects with MCI had an alteration in myo-Inositol signal, with significantly higher value of myo-Inositol/Creatine ratio (mI/Cr) than control subjects and similar to subjects with mild AD, who instead had a significant reduction of N-Acetyl-Aspartate/Creatine ratio (NAA/Cr) level in the paratrigonal white matter compared to controls. Consistently, Kantarci et al. [60] showed in the gray matter of posterior cingulate gyrus an increased mI/Cr level in subjects with MCI compared to normal controls and higher still in patients with AD, as well as a lower NAA/Cr in AD compared to both MCI and cognitively normal subjects. On the contrary, Chantal et al. [25] suggested that the increased mI signal is a neurochemical abnormality associated with AD but not with MCI, with a significant increased mI signal in patients with AD compared to both MCI and control subjects.

BIOMARKERS

Biomarkers other than those obtained from structural or functional neuroimaging were widely studied in subjects with early AD. Typical neuropathological lesions of AD are senile plaques, constituted by the beta-amyloid protein, and neurofibrillary tangles, originating from hyperphosphorylated tau protein [5]. Over the last years, many efforts have been made in the identification of potential biomarkers for both MCI and de-

mentia from the analysis of cerebral spinal fluid (CSF). CSF biomarkers for MCI include total tau protein (T-τ), phosphorylated tau protein (P-τ) and amyloid beta 1-42 protein (Aβ-42) [5,116]. Several studies have found high CSF T-τ and P-τ, and low CSF Aβ-42 in subjects with MCI, with sensitivity figures similar to, or slightly lower than, those found in AD cases [6,7,9, 66].

These biomarkers also showed a high sensitivity in differentiating early AD from normal aging, depression and Parkinson's disease, but lower specificity versus other dementias, such as fronto-temporal and Lewy body dementia [5].

Recently, it was suggested that also plasma Aβ-42/ Aβ-40 ratio may be a useful marker for identifying cognitively healthy elderly subjects who are at increasing risk for developing MCI and AD, reflecting the extent to which there has been selective aggregation and deposition of Aβ-42 in the brain [50]. The authors postulated that CSF Aβ-42, as well as plasma Aβ-42 levels, decline in parallel as Aβ-42 deposits in the brain, and, because Aβ-42 aggregation and deposition precedes MCI and AD, most subjects who develop MCI/AD have a low Aβ-42/ Aβ-40 ratio several years before the diagnosis of the disease.

There is also evidence for a role of oxidative stress in the pathogenesis of MCI [22,62,78,83,107]. Increased levels of the isoprostane 8,12-iso-PF2a-VI -a specific marker of in vivo lipid peroxidation [108] – were found to be significantly elevated in CSF, plasma and urine of MCI subjects compared with controls [107], suggesting that lipid peroxidation may be an early event in the pathogenesis of the disease. Nevertheless, additional studies on the presence of elevated levels of biomarkers of oxidative stress in MCI are warranted, also in light of the discrepancies otherwise observed between brain/CSF versus plasma/urine F2-isoprostanes and F4-neuroprostanes levels [90,109].

An increased DNA oxidative damage in peripheral leukocytes, previously reported in AD subjects [81,82], has been recently found in MCI [85], as well as in nuclear and mitochondrial DNA isolated from frontal, parietal and temporal brain lobes [127].

Subjects with MCI showed also lower levels of non enzymatic antioxidants (vitamin A, vitamin C, vitamin E, uric acid and of the carotenoids lutein, zeaxanthin and β-carotene) and lower activities of enzymatic antioxidants (plasma and erythrocyte superoxide dismutase, plasma glutathione peroxidase) as compared to controls [110]. Similarly, plasma total antioxidant capacity (including uric acid, glutathione, thiol groups, vitamins, glutathione peroxidase, superoxide dismutase and catalase) was shown to be significantly reduced in MCI subjects as compared to age-matched controls [53].

Finally, it was recently found a decrease in the percentage of total lymphocytes and a concomitant increase in granulocytes in MCI subjects compared to controls [75], consistent with evidences of a decrease in the proliferative ability of lymphocytes [117], and of increased granulocyte activity [69] in AD patients, suggesting an inflammatory state specific not only for AD, but also for MCI.

PREDICTORS OF PROGRESSION OF MCI TO DEMENTIA

Clinical, imaging, genetic and CSF aspects have been widely examined as possible markers in MCI in order to detect subjects at greater risk of conversion to dementia. However, most of the studies describe subjects with aMCI, with negligible information for other MCI subtypes. Some authors have also tried to combine different predictors to increase the accuracy of conversion to AD or other dementias.

Neuropsychological predictors of conversion include performance on specific cognitive tests, particularly those assessing delayed recall and executive functions [3,27,122]. However, neuropsychological tests rarely overcome 70% sensitivity and specificity [88]. Conversely, Visser an colleagues [126] found that scores on memory tests predicted progression to AD with 88% accuracy, and the addition of hippocampal volume measure increased accuracy to 100%. Other clinical aspects considered as predictors of conversion are IADL disability [96], depressive symptoms [87], and coexistent motor dysfunctions. For this aspect, in a recent longitudinal cohort study in subjects with MCI, impaired motor performance of lower limbs, parkinsonian gait, and bradykinesia increased the risk of AD after a ten-year follow-up [1].

Hippocampal or entorhinal atrophy on MRI are the most commonly used neuroradiological markers of conversion from MCI to dementia [116]. Subjects with MCI who converted to AD during two-year follow-up, in fact, had a greater atrophy in the left entorhinal cortex, bilateral superior temporal gyri, and right inferior frontal gyrus compared to nonconverters [16]. Similarly, data from the Rotterdam study showed that hippocampal and amygdala volumes were strongly asso-

ciated with the risk of dementia in cognitively intact elderly people after six-year follow-up [33].

Recent promising neuroimaging techniques for evaluating conversion from MCI to dementia include PET and ^{1}H-MRS. Reduced metabolic activity in temporoparietal cortices [10] or in the posterior cingulate gyrus [36], as shown in FDG-PET scans, have been associated with a greater risk of progression to dementia. Further, the highest degree of accuracy (>90%) was achieved by means of PET scan plus either memory performance [4] or APOE ε4 genotype [92].

A recent study performed with ^{1}H-MRS found that subjects with aMCI who convert to AD over one year had a significant difference of the NAA/Cr ratio in the left hemisphere with respect to both non-converters and healthy controls [84]. These data confirmed previous evidence suggesting that decreased NAA/Cr levels predict future conversion to AD in subjects with MCI [26, 86]. It was recently reported that while there were no differences in NAA/Cr, Cho/Cr and mI/Cr at baseline between stable MCI and MCI who converted to AD after a median follow-up period of thirteen months, the annualized rate of change in Cho/Cr ratio was greater in stable MCI compared to converter MCI and cognitively normal controls, suggesting a possible compensatory mechanism in stable MCI [61].

CSF biomarkers represent to date those with the highest accuracy for the conversion from MCI to AD. Three biomarkers – T-τ protein, P-τ protein and Aβ-42 protein – have been evaluated in many scientific reports. Subjects with MCI who lately developed AD had an increased baseline CSF concentration of T-τ and P-τ, whereas the level of Aβ-42 protein was decreased. In addition, recent studies provided evidence that reduction in the Aβ-42/P-τ ratio may help to identify those patients with MCI who later develop AD [5,116]. However, the clinical follow-up in these studies has been short and data have been collected in small selected hospital samples. To overcome this issue, data from a recent article, carried out in 180 consecutive individuals with MCI over a four- to six-year of follow-up, showed that subjects with MCI who had pathological concentrations of T-τ and Aβ-42 proteins at baseline are at increased risk to develop AD. The association between pathological CSF findings and progression to AD was independent of APOE genotype, age, gender, and education. The combination of T-τ and Aβ-42/P-τ ratio yielded closely similar results with a sensitivity of 95% and a specificity of 87% [55]. CSF T-τ/Aβ-42 and P- τ/Aβ-42 ratios were recently identified as good biomarkers that predict future dementia also in cognitively healthy old subjects [37].

Some studies have tried to identify non-CSF peripheral markers of MCI. Among those, platelet forms of amyloid precursor protein have been proposed. At two-year follow-up MCI subjects who converted to AD showed a significant decrease of baseline platelet APP forms ratio compared to nonconverters, with a sensitivity of 83% and a specificity of 71% [20].

Among genetic predictors, the APOE ε4 allele, the only genetic factor associated with an increased risk of sporadic AD [38], was described to be associated with conversion from MCI to dementia. Data from the Mayo Clinic cohort, which is a relatively young group, demonstrated that APOE ε4 genotype is the best predictor of conversion to dementia [101]. These findings were recently confirmed by a longitudinal cohort study in which the presence of at least one APOE ε4 allele affected the transition from cognitively normal aging into amnestic MCI or into dementia [64]. According to these data, APOE ε4 may represent a predictor of dementia only for aMCI but not for other MCI subtypes.

TREATMENT AND PREVENTION

Early treatment of mild to moderate AD is associated with a better response than late treatment [130], so it is conceivable that treating MCI may be most effective in delaying progression to AD. However, to date there is no proven pharmacological approach for MCI. Antioxidants, including Ginkgo Biloba, selegiline and vitamin E, have been proposed for delaying the progression to dementia, but their usefulness is unclear [80]. In randomized clinical trials, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), antioxidant (vitamin E), anti-inflammatory drugs (rofecoxib), and nootropics (piracetam) failed to prevent progression of MCI to dementia [58]. In a randomized clinical trial of three years of observation, donepezil showed a transient preventive effect after one year, particularly in subjects who had at least one APOE ε4 allele, but efficacy was lost at the end of the study [102], so evidence is not strong enough for recommending its routine use [114].

Management of subjects with MCI is currently non specific: control of vascular risk factors, treatment of a concomitant condition such as depression or hypothyroidism, and reduction in the use of anticholinergic drugs have been proposed [47]. Epidemiological data suggests that moderate exercise and physical activity, such as walking three times a week, are associated with a lower risk of dementia [105]. According to these findings, a randomized controlled trial examining the effect

of a walking program and vitamin B supplementation on the rate of cognitive decline in older adults with MCI is currently ongoing [124]. In addition, recent data suggest that an active and socially integrated lifestyle in late life protects against dementia and AD [45]. In the Bronx Aging Study, participation in cognitive activities was associated with a lower risk of development of MCI, even after excluding individuals at early stages of dementia [125]. Since it seems evident that memory and attention training is beneficial in normal elderly persons [13] and in patients with early AD [29], cognitive training may have a role in subjects with MCI in slowing down further decline and should be explored in future clinical trials. Encouraging results, in fact, have been reported from uncontrolled studies [54]. Finally, clinicians should pay close attention to control for modifiable cardiovascular risk factors, including blood pressure, diabetes, and lipid profile, all factors that have been associated with an increased risk of dementia.

CONCLUSIONS

MCI is a syndrome at high risk for dementia and not a definitive diagnosis of a disease. It represents a condition with multiple sources of heterogeneity, including clinical presentation, etiology, and prognosis. The majority of data present in the literature refer to aMCI and very few concern other subtypes of the condition. According to these data, aMCI seems to represent an early stage of AD, while the outcomes of the other MCI forms are more heterogeneous.

It might be time to consider revisions of the ICD and DSM to include specific diagnostic criteria for MCI. Furthermore, an update of the NINCDS-ADRDA criteria for AD should include a prodromal stage of Alzheimer's disease that defines MCI. Current criteria for MCI should be updated to include restriction in complex ADL. There is a need for sensitive tools able to detect subtle modification in cognitive and functional abilities also to implement a primary prevention trial in non demented subjects. With this aim the Alzheimer's Disease Cooperative Study Instrument Committee has recently developed new assessment instruments that can be self-administered and/or do not require significant involvement of professional staff [41].

The diagnostic and prognostic role of specific behavioral symptoms (i.e. depression), somatic conditions and motor dysfunctions need to be better clarified. There is not enough evidence to recommend specific predictors for the conversion from MCI to AD. The combined use of cognitive tests, APOE genotype, and neuroimaging techniques is probably the best option for prediction purposes, but further studies are needed to define the sensitivity and specificity of this global approach for recommending its routine use at the screening level.

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