

OUTCOME FOR SECONDARY PREVENTIVE TRIALS (IN MILD COGNITIVE IMPAIRMENT)

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Abstract: Preventive trials should first target specific patients' groups, and growing information concerning evolution of patients with mild cognitive impairments should be used for a proper selection. Studies on clinical evolution may also help to select appropriate neuropsychological tests, and prevention can be defined as maintained performance on a battery of tests. Disturbance of daily living activities should be considered since it defines occurrence of dementia. Complementary information can be obtained from behavioural evaluation, neuroimaging and biological markers.

Introduction

A short review of interesting outcomes for studies concerned with "mild cognitive impairment" (MCI) is presented. The review is by no way exhaustive and selected suggestions provided in this summary should be discussed in the light of preliminary results from ongoing studies. It must be emphasized that many outcomes are centred on evolution to Alzheimer's disease (AD), while the heterogeneous syndrome of MCI may evolve to other forms of dementia.

Definition of the population

The population of patients with "Mild Cognitive Impairment" is heterogeneous. Patients have been described with isolated amnesic impairment, with executive deficit or with difficulties in multiple cognitive domains, but without dementia. In subjects older than 65 years, the prevalence of MCI with multiple domains impairment (6%) might correspond to the prevalence of amnesic MCI (5%) (13). Consequently, a single neuropsychological tool would not cover the range of cognitive difficulties nor their variable evolution in the syndrome. Importantly, it is not easy to select MCI subjects who will evolve to AD versus those who might "naturally" remain stable (18). One must keep in mind that stability may occur in MCI without any therapeutic intervention.

Natural evolution of patients with MCI

Clinical evolution

The rate of "conversion" of MCI patients to dementia is variable, and it depends on criteria used for the population selection. Apart from non-amnesic MCI "multi-domain", who may evolve to non-Alzheimer dementia, the other "subtypes" of MCI are likely to convert to AD (2). Questions from the Clinical Dementia Rating (CDR) questionnaire may help to predict conversion of MCI to AD (3). A better naming performance is observed in elderly subjects with stable MCI compared to converters (11), and this is true also for episodic

memory performances. This suggests (as expected) that the initial level of cognitive performance would help to select patients with a higher risk of evolution to dementia.

Evolution of brain imaging

The evaluation of medial temporal atrophy predicts conversion of MCI to AD (4). Brain FDG-PET also predicts conversion of MCI to AD (5), and PET images showing accumulation of cerebral amyloid protein provide interesting information on AD pathology. Since brain lesions in AD precede clinical symptoms of dementia, abnormalities on neuroimaging studies might help to select patients with a higher risk of evolution to dementia.

Brain pathology

Amyloid plaques and tangles are observed in patients with questionable AD (9, 10), and many subjects with a CDR 0.5 evolve to AD (14). This justifies that most outcomes in this review are related to characteristics of dementia of the AD type.

Outcome for trials with MCI

Cognitive testing

A lot of different tests assessing memory, attention, executive function and psychomotor speed were used in the literature in trials for MCI, and smaller deficits in verbal abilities and visuospatial skills were reported in preclinical AD (1). Classical ADAS-cog and MMSE were also used (12, 16).

The free and cued selective reminding test might be particularly interesting. Survival analyses of 264 non-demented participants indicated that poor performance on free recall measures of this memory test controlling word encoding best predicted the conversion to dementia in the sample. In the same vein, the free recall score of this task is able to make the distinction between patients at the early stage of AD and MCI non converters. More interestingly, the performance for cued recall decreases from MCI stage to mild, and then to moderate AD stage (17). Maintenance of cued recall performance might reflect stabilization of the AD pathological process.

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Since multiple cognitive domains may be impaired in MCI, a compound score combining performances for different tests would be useful (using z-scores and validated tests) (6, 8). A review of longitudinal studies in MCI and multivariate analyses would be necessary to discuss the selection of neuropsychological tests that best describe the progressive evolution of MCI to dementia.

Moreover, slopes would describe decrease in cognitive performances more accurately than differences between timely assessment.

Global functioning

The CDR questionnaire might be used to assess Clinical Global Impression of change. Caregivers may bear witness of the evolution of the patient's performances, and their assessment is frequently correlated with a global evaluation of cognitive impairment.

IADL Questionnaires

Questionnaires assessing instrumental activities of daily living (IADL) were already proposed to assess evolution of MCI patients, such as Complex Activities of Daily Living – Prevention Instrument (7) or Functional activities questionnaire (12). It might be important that some questions remain open to specific or rare activities in which individual patients might have expertise. A progressive impairment in rare activities might be an important clue for disease evolution.

MRI and PET

Neuroanatomical imaging, FDG-PET or amyloid PET (or even other neuroimaging methods) could be used to assess a decrease in pathological evolution in MCI. FDG-PET (or SPECT measures of cerebral blood flow) may be influenced by many symptomatic treatments (with acetylcholinesterase inhibitors for example). Measuring N-acetylaspartate (NAA) with MRI might indicate preserved integrity of local neurons. Measures of sensitivity, specificity and predictive values might help to select the best marker of disease evolution to AD.

Those markers might not be useful for patients evolving to another disease.

Biological markers

Measures of cerebrospinal fluid (CSF) concentrations of beta-amyloid or phosphorylated tau protein do reflect brain AD pathology. Blood measurement are also suggested to reflect accumulation of cerebral lesions in AD. Since CSF beta-amyloid is decreased in AD, the interpretation of changes in concentration might be difficult. Longitudinal studies need to be "meta-analysed" to pick up the most interesting marker of "brain protection" against AD.

Psychological and behavioural evaluation

Information on psychological and behavioural symptoms (obtained with the Geriatric depression scale or the Neuropsychiatric interview) might provide important clues concerning the evolution of MCI patients to psychiatric or neurological diseases. Information from the patient and a collateral source would be important to obtain complete information on depressive symptoms (15).

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