Therapeutical strategies in mild cognitive impairment

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Rezumat

Cresterea sperantei de viata este asociata cu cresterea numarului de varstnici cu dementa. Deficitul cognitiv usor, descrie o deteriorare a functiilor cognitive- in special a memoriei- este un stadiu de tranzitie intre tulburarile cognitive asociate varstei si dementa usoara, majoritatea tipurilor de dementa fiind precedate de o stare prodromala de deteriorare cognitiva usoara. Aproximativ 50-80% din pacientii cu deteriorare cognitiva usoara dezvolta in evolutie dementa. Un procent de 6-12% din pacienti evolueaza spre dementa in decursul unui an. Cunoscand riscul de progresie spre dementa acesti pacienti ar trebui evaluati periodic si monitorizati pentru prevenirea evolutiei spre dementa. Scopul acestei lucrari este de a trece in revista datele existente despre tratamentul recomandat pentru deficitul cognitiv usor.

Abstract

Increasing life expectancy has been associated with an increase in the number of old people with dementia. Mild cognitive impairment (MCI) describes the slight impairment in cognitive function—typically memory—that is thought to be a transitional state between the cognition of normal aging and mild dementia. Approximately 50-80% of MCI patients develop dementia during the later course (Peterson et al 1999, 2001a, 2001b). Between 6 and 25% of MCI patients progress to dementia or AD each year. MCI patients should be evaluated regularly for progression to AD. Knowing the risk for conversion is important because we can inform the patients and their relatives, we can give advice for preventing strategies and also we can treat MCI as to reduce de risk for conversion to dementia. Our aim was to review the data on recommended treatment for MCI.

INTRODUCTION

Mild cognitive impairment is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life, subjects perform more poorly on a variety of cognitive, functional and behavioral measures than normal person of the same age. Mild cognitive impairment encompass the clinical state between normal cognition and dementia in elderly people, most types of dementia are preceded by a recognizable phase of mild cognitive decline. The incidence of MCI in adults over 65 in the Unites states is estimated to range from 8 to 58 individuals per 1000 per year. The prevalence of MCI varies between 2 and 30% in the general population and between 6 and 85% in a clinical setting (average 40%) (Visser, 2000). Studies with a short to intermediate follow-up period (average 3.1 years, range 1.1–5 years) indicated that on average 10% (range 2–31%) of the subjects with MCI developed dementia at each year of follow-up (Bruscoli and Lovestone, 2004).

Criteria for MCI

- memory complaint, preferably corroborated by informant
- impairment is 1.5 standard deviations (SD) below peer norms
- impaired memory function for age and education
- preserved general cognitive function
- intact activities of daily living
- not demented (Peterson et al 1999, 2001a, 2001b)

Mild cognitive impairment can have several different underlying causes, such as depression or other psychiatric disorder, metabolic or medical disorder, trauma, substance abuse or medication reactions. Diabetes, hypertension, hypercholesterolemia, atherosclerotic cerebrovascular disease, obesity are associated with a increased risk of dementia. Patients with these condition should be closely monitored because of their increased risk for dementia. Comorbid neuropsychiatric conditions

including apathy, depression, anxiety and irritability are seen in up to 80% of MCI patients over time.

TREATMENT OF MCI

The treatment of mild cognitive impairment has been the subject of a number of recent chapters and reviews. There have been relatively few randomized controlled trials of any therapy sufficient to rank as level 1 evidence. Nevertheless, there are a number of potential interventions, both non-pharmacological and pharmacological, that deserve to be addressed.

The choice of medication depends on the severity of the disease. In some cases a combination of medications is used.

NONPHARMACOLOGICAL TREATMENT

Nonpharmacological treatment refers to treatment of comorbid conditions, physical activity and cognitive interventions.

There are many conditions that can produce mild cognitive impairment or exacerbate memory loss in mild cognitive impairment. Patients with sleep disorders often present with memory loss, cardiovascular disease, abnormal blood pressure, either too high or too low, low levels of physical, social and mental activity, fewer years of education , history of depression. People who have higher levels of social, mental and physical activity seem to have less risk of MCI and dementia.

A clinical study, publicated in the last number of Journal of the American Medical Association, demonstrated that regular physical activities seems to improve the memory loss to persons over 50 with cognitive impairment. This study is the first one which prove that physical exercises improve the cognitive functions to elderly with mild cognitive impairment.The patients enrolled in this study presented risk factors for dementia and they had memory decline, they have had to practice 150 minutes per week regular physical training physical activity tree times/ week, 50 minutes each time. The cognitive functions were evaluated 18 months with ADAS (Alzheimer's disease Assessment Scale). The study demonstrated that the benefits of regular physical exercises persisted at least 12 months after the end of the study.

There is evidence for the role of lifestyle and environmental factors as moderators of differences in cognitive aging and as protective agents for development of Alzheimer's disease. These factors are engagement in professional and leisure activities, education, expertise and experience. Cognitive stimulations refers to involvement in group activities that are designed to increase cognitive and social functioning: discussions, supervised leisure activities, list memorization with no particular support and other structured activities; cognitive training includes repeated problems and exercises, teaching strategies that exploit spared cognitive capacities to improve impaired ones.

Several epidemiologic studies have shown an association between vascular risk factors and cognitive impairment. Results from 3 clinical trials have supported the role of treatment of hypertension in reducing the risk of cognitive decline in elderly people without dementia, some of whom had mild cognitive impairment. The Syst-Europe randomized controlled trial involved 2418 older people with isolated systolic hypertension and showed a 50% decrease in cases of dementia after 2 years in the treatment group compared with the control

group. By extrapolation of these results, if 1000 hypertensive patients were treated with antihypertensive drugs for 5 years, 19 cases of dementia might be prevented. Another study of blood pressure reduction in elderly people with cerebrovascular disease resulted in significant but less impressive reduction in cognitive decline and dementia. The third clinical trial compared captopril and bendrofluazide in people with mild cognitive deficits. Patients with the best response to treatment in terms of reduction of their diastolic blood pressure showed significant improvement on 2 cognitive tests.

Findings from these 3 studies suggest that the reduction of blood pressure in elderly patients with hypertension who have mild cognitive impairment is not hazardous. The evidence that treating other vascular risk factors will reduce subsequent dementia is meager. Trials of primary prevention with statins, for instance, did not provide any evidence of benefit on cognitive function. We recommend treatment of vascular risk factors, including hypertension, as an effective means of preventing progression to dementia in patients with mild cognitive impairment

Lifestyle changes also may reduce your risk. Adherence to a Mediterranean diet is associated with lower incidence of MCI and with lower incidence of progression to dementia. adherence to a Mediterranean diet seems to improve carbohydrate metabolism and significantly reduces plasma glucose levels, serum insulin levels, and insulin resistance, which may explain its beneficial effects on lowering incident MCI. Mediterranean diet is a diet based on consume of fruit and vegetables, olive oil, grains, fish and poultry, food rich in antioxidants and omega 3.

PHARMACOLOGICAL TREATMENT

Several classes of drugs have been studied for the prevention of progression to dementia, these include cholinesterase inhibitors, antioxidants, nootropics, anti-inflammatory agents and other drugs which modify brain chemical levels.

CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors are typically used to treat the early and middle stage symptoms of diseases such as Alzheimer's. This is because the deterioration in the production of acetylcholine accelerates over time, as more and more brain cells become damaged Treatment strategies for AD could be extrapolated to interventional strategies in MCI. These include donepezil (Aricept R), rivastigmine (Exelon R), galantamine (Reminyl R), and tacrine (Cognex R).

Tacrine, the considered a first generation of cholinesterase inhibitor, is no longer used due to adverse events.

Donezepil, the second cholinesterase inhibitor, is approved for treating mild dementia. The maximum daily dose of donepezil is normally 5–10 milligram (mg). This dose is taken just once a day, either in the morning or in the evening. It is well tolerated, the adverse events observed after administration includes nausea, vomiting, headache, insomnia and dizziness.

Rivastigmine is a reversible acetylcholinesterase and butyrylcholinesterase inhibitor and was found to be superior to placebo in clinical trials. The maximum daily dose of rivastigmine is 6–12 mg. The drug is taken twice a day with meals (typically breakfast and dinner).

Galantamine has a dual mechanism of action, an cholinesterase inhibitor and

has additional properties at nicotinic receptors, increasing cholinergic activity by activating presynaptic nicotinic receptors. The maximum daily dose of galantamine is 16–24 mg, and it is also taken twice a day with meals. The side effects are usually gastrointestinal related, like nausea, vomiting, dihareea.

Cholinesterase inhibitors improve or at least retarding the rate of loss of cognition, the drugs can improve a person's quality of life.

Other potential therapies being considered for MCI are similar to others being explored for Alzheimer's, including: antioxidants, anti-inflamatory agents, hormonal treatment and drugs that alter brain chemical levels.

ANTIOXIDANTS

Substances such as vitamin E and ginkgo biloba may protect brain cells from the oxidative stress that appears to play a role in Alzheimer's, but there's little evidence that either is effective in preventing MCI from progressing to dementia. Ginkgo biloba has been used medicinally for thousands of years. Ginkgo is used for the treatment of numerous conditions, many of which are under scientific investigation. Available evidence demonstrates ginkgo's efficacy in the management of Alzheimer's/multi-infarct dementia and may be as helpful as acetylcholinesterase inhibitor drugs such as donepezil (Aricept R). Well-designed research comparing ginkgo to prescription drug therapies is needed.

Vitamin E is a dietary compound with antioxidant properties involved in scavenging free radicals. Laboratory and animal studies have pointed towards a possible role for Vitamin E in the prevention and management of cognitive impairment

In 2005 the Results of study ADSC (Alzheimer's Disease Cooperative Study) showed that treatment with the antioxidant vitamin E could delay the time to important milestones in patients with moderately severe Alzheimer's disease. The present study was designed to determine whether treatment with vitamin E or donepezil, the most widely used cholinesterase inhibitor available at the time the study was designed, could delay the clinical diagnosis of Alzheimer's disease in subjects with the amnestic form of mild cognitive impairment." The combination supplemental of vitamin E(400UI/day or more) and vitamin C (at least 500mg/day of ascorbic acid) but not either vitamin alone reduce significantly the incidence and prevalence of dementia. There are clinical trials looking at vitamine E plus selegiline (a monoamine oxidase inhibitor) as a treatment for dementia and for preventing progression of cognitive impairment.

NOOTROPICS AGENTS

Nootropics are drugs that boost brain activity an d memory. Nootropics enhance the brain function. Piracetam is the most used nootropic, increases performance in a variety of cognitive tasks, appear to be effective in dementia and mild cognitive impairment. The dose of piracetam used for cognitive decline is 1600mg/day. The side effects are few, transient and mild.

ANTI-INFLAMMATORY AGENTS

Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce inflammation in the brain. Most convincing to many investigators and clinicians is the fact that epidemiological studies show that individuals who use anti-inflammatory drugs have a reduced risk of developing AD.

There are studies which doesn't prove any significant benefits of NSAIDs to patients with mild cognitive

impairment. The anti-inflammatory agents used in MCI clinical trials are ibuprofen, rofecoxib and celecoxib. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment, results from this MCI study did not support the hypothesis that rofecoxib would delay a diagnosis of AD. In conjunction with the lack of effects observed in previous AD studies, the findings suggest that inhibition of COX-2 is not a useful therapeutic approach in AD.

STATINS

Hypercholesterolemia increase the risk of cerebrovascular disease and is a risk for Alzhemeir disease by stimulating the production of amyloid. Statins decrease cholesterol level by inhibiting production in the liver and may also have direct effects an Aβ metabolism in the brain by activating α-secretases. Clinical studies have shown improvement of cognitive impairment after treatment with statins (simvastatin, atorvastatin and pravastatin).

DRUGS THAT ALTER BRAIN CHEMICAL LEVELS

Medications more commonly used to reduce the symptoms of Parkinson's disease may help normalize the effects of mild cognitive impairment.

HORMONAL TREATMENT IN MCI

Replacing the estrogen lost at menopause can prevent many of the manifestations of aging including osteoporosis, cardiovascular disease and decline in cognitive functions. Hormone replacing therapy after menopause have benefits for menopausal symptoms, for cognitive function – neuroprotective inhibit neuronal apoptosis and modulate Apolipoprotein gene expression.

CONCLUSIONS

MCI is a a classification reserved to elderly persons with an increased risk for developing dementia. Treatment of this condition – MCI – is important to prevent Alzheimer's disease or to stop the progression of this condition.

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