

Antioxidants for the treatment of mild cognitive impairment

Neurological Research, Volume 26, July, 2004 pp. 598–602

P. Mecocci, E. Mariani, V. Cornacchiola and M. C. Polidori

FROM ABSTRACT:

The isolated deficit in recent memory frequently associated with decline to Alzheimer's disease (AD) is defined as mild cognitive impairment (MCI).

The observed progression of MCI to AD suggests a common pathogenesis between these two clinical syndromes, and several neuroimaging, neuropsychological and biological methods are applied with the purpose of identifying subjects at risk of AD.

Among these methods, the evaluation of a condition of oxidative stress is gaining increasing attention.

Since oxidative stress seems to be involved in the earliest phases of AD, and MCI may be considered as a prodromal phase of dementia, it is an attractive issue to focus therapeutic interventions on the early phase of the disease.

THESE AUTHORS ALSO NOTE:

"Alzheimer's disease (AD) is the most common cause of dementia in the elderly and it is estimated to affect 4 million people in the US and 4.8 million in Europe, its incidence doubling every 5 years beyond the age of 65 years."

"It is known that the pathological changes in AD begin years before a clinical diagnosis can be made, and there is a large body of evidence suggesting that the condition termed 'mild cognitive impairment' (MCI) may represent this pre-clinical stage."

"MCI refers in fact to persons whose memory or other cognitive abilities are not normal, but who do not have clinically diagnosed dementia."

It is during this MCI phase that interventions to slow, halt, or reverse the pathological processes involved might be most effective in reducing DA.

These authors present the most recent results on the role of oxidative stress in AD and in MCI as well as on the proposed role of antioxidants in the prevention and therapy of MCI and AD.

MCI is defined as a "condition in which memory complaint and abnormal memory function for age and education coexist with normal function in the activities of daily living, normal general cognitive function, and absence of dementia."

THE ROLE OF OXIDATIVE STRESS IN AD AND MCI PATHOPHYSIOLOGY

AD is characterized by:

- 1) Synaptic loss.
- 2) Nerve cell loss (mostly in the cerebral cortex, hippocampus and amygdala).
- 3) Extracellular deposition of b-amyloid protein.
- 4) Levels of acetylcholine within synapses decline.

It is thought that the biochemical mechanism of the pathogenesis involves mitochondrial dysfunction and neuro-inflammatory processes. **[IMPORTANT]**

"Among these interrelated mechanisms finally leading to programmed cell death cascades, one gathering much attention is the production of reactive species of oxygen (ROS), nitrogen (RNS) and chlorine (RCS)."

The early development of a condition of oxidative stress is the key step involved in the pathogenesis of AD, and it also constitutes a process bridging the degeneration of the AD brain with its cerebrovascular impairment.

AD patients lack the highly anastomosing array of vessels in the brain microvasculature that is seen in normal people.

Oxidative stress is linked to known risk factors for AD, including aging, stroke, heart disease, type 2 diabetes, head trauma, and smoking.

AD patients have markedly poor antioxidant status and function when compared with controls.

The "evidence for the role of oxidative stress in the pathogenesis of AD is extensive and solid."

Specific markers of lipid peroxidation are found to be significantly elevated in CSF, plasma and urine of MCI subjects as compared with controls, "suggesting that lipid peroxidation is an early event in the pathogenesis of the disease."

An accumulation of oxidative damage in the mitochondria might constitute a continuous source of free radical damage and the progression of MCI to AD.

[VERY IMPORTANT]

MCI and AD subjects have lower levels of non-enzymatic antioxidants (vitamin A, vitamin C, vitamin E) and of the carotenoids lutein, zeaxanthin and b-carotene.

Patients with MCI and AD showed similarly lower activities of plasma and erythrocyte superoxide dismutase as well as of plasma glutathione peroxidase as compared with controls, suggesting that subjects developing MCI and subsequently AD may have an antioxidant enzymatic activity inadequate to counteract the hyperproduction of free radicals during a recently established condition of oxidative stress. [Interestingly, low level lasers increase the productions of these enzymes].

PREVENTIVE AND THERAPEUTIC USE OF ANTIOXIDANTS IN AD AND MCI

“Various antioxidant therapies have been tested and have shown to affect the onset as well as the progression of AD.”

Vitamin E prevents the accumulation of oxidative metabolites and therefore its neurotoxicity.

“Vitamin E administered in large doses plays a neuroprotective role, and it has therefore been proposed for the prevention and treatment of AD.”

The high intake of vitamin E and vitamin C from food is associated with a lower incidence and prevalence of AD.

The intake of high doses of vitamin C and E supplements was related to a lower risk for AD.

“Vitamin E intake from foods and supplements was also found to be associated with less cognitive decline with age.”

“A reduced risk of dementia has been also found in association with increased intake of flavonoids.”

Mitochondrial antioxidants are effective in slowing AD progression.

In mild to severely demented patients, ginkgo biloba appeared capable of stabilizing and improving the cognitive performance, and the social functioning of demented patients.

A recent study showed that a 52-week treatment with 1120 mg of ginkgo biloba in demented patients resulted in a mild, but significant, improvement in cognitive assessment.

[Le Bars PL, Velasco FM, Ferguson JM, et al. Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer’s disease. *Neuropsychobiology* 2002; 45: 19–26]

Treatment with 600 mg of alpha-lipoic acid daily for 337 days led to a stabilization of cognitive function, in a group of AD and other dementia patients.

In patients with mild to moderate dementia, supplementation with cobalamin and folate improved cognitive function.

Others have noted cognitive improvement with supplementation of 3-8 g/day of thiamine.

"Since oxidative stress seems to be involved in the earliest phases of AD, and MCI may be considered as a prodromal phase of dementia, it is an attractive issue to focus therapeutic interventions on the early phase of the disease."

Importantly, early administration of vitamin E suppresses brain lipid peroxidation and significantly reduces levels of amyloid plaque deposition. However, if vitamin E supplementation is started at a later time point, when amyloid plaques are already deposited, no significant benefit is observed. "This suggests the possibility that vitamin E could be more effective if administered in the earliest possible stage of the disease process."

"The use of a single antioxidant may not be optimal for quenching all the various types of free radicals that are produced in the AD brain."

"An increased intake of antioxidant micronutrients from fruits and vegetables is the best currently available strategy to prevent cognitive impairment."

KEY POINTS FROM DAN MURPHY

- 1) Mild cognitive impairment (MCI) is an isolated deficit in recent memory and is often associated with decline to Alzheimer's disease (AD).
- 2) Free radical production causes oxidative stress and is involved in the earliest phases of MCI and AD.
- 3) Alzheimer's disease (AD) is the most common cause of dementia in the elderly and it is estimated to affect 4 million people in the US.
- 4) The incidence of Alzheimer's disease is doubling every 5 years.
- 5) Mild cognitive impairment (MCI) is a pre-clinical stage of AD.
- 6) Free radical production and oxidative stress cause synaptic loss, nerve cell loss, amyloid protein deposition, and decline in brain acetylcholine neurotransmitter.
- 7) Free radical production causes oxidative stress, mitochondrial dysfunction and neuro-inflammatory processes.
- 8) AD patients have markedly low antioxidant levels compared with controls.
- 9) The evidence for a role of oxidative stress and free radicals in the pathogenesis of AD is extensive and solid.
- 10) Lipid peroxidation is an early event in the pathogenesis of the MCI.
[Take your antioxidant co-factors, Nutri-west, 800-443-3333]

- 11) An accumulation of oxidative damage in the mitochondria might constitute a continuous source of free radical damage and the progression of MCI to AD.
- 12) MCI and AD subjects have lower levels of non-enzymatic antioxidants like vitamin A, vitamin C, vitamin E, and carotenoids lutein, zeaxanthin and b-carotene.
- 13) Patients with MCI and AD have lower levels of antioxidant enzymes (superoxide dismutase, glutathione peroxidase) as compared with controls. [Interestingly, low level lasers increase the productions of these enzymes].
- 14) The following antioxidants slow the progression of Alzheimer's disease.
- A) Vitamin E
 - B) Vitamin C
 - C) Increased intake of flavonoids
 - D) Mitochondrial antioxidants (like CoQ10)
 - E) Ginkgo biloba
 - F) Alpha-lipoic acid (600 mg/day)
 - G) Vitamins B12, thiamine, and folate
- 14) The use of a single antioxidant is not optimal for quenching all the various types of free radicals that are produced in the AD brain.
- 15) An increased intake of antioxidant micronutrients from fruits and vegetables is the best currently available strategy to prevent cognitive impairment.