

Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

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The Cholesterol-Cognitive Impairment Connection

According to the American Heart Association, an estimated 99.9 million American adults have borderline-high cholesterol levels of 200 mg/dL and higher and about 34.5 million of these are considered “high-risk” with levels of 240 mg/dL or above. High Cholesterol is a risk factor for cognitive impairment and Alzheimer’s Disease. In this issue we examine the connection between cognitive impairment and LDL cholesterol. Future issues will examine the impact of HDL cholesterol on cognitive impairment.

Cholesterol and Cognitive Impairment: Clinical Evidence

Elevated LDL cholesterol is a well known risk factor for atherosclerosis, which can lead to peripheral vascular disease, coronary artery disease, stroke, cognitive impairment and dementia due to cerebrovascular disease (**VD**). Elevated LDL cholesterol can also increase risk for dementia due to Alzheimer’s Disease (**AD**). Clinical evidence for these conclusions is discussed below.

In the Rotterdam prospective study, the diets of 5,386 normal aging persons were assessed and subjects were followed for a mean of 2.1 years. Persons with high intake of total fat, saturated fat or cholesterol were, respectively, 2.4, 1.9, and 1.7 times more likely to develop dementia. Vascular dementia was more related to total or saturated fat¹.

A four year study of 1,037 women under 80 years old with coronary artery disease without hysterectomy² found that women with LDL cholesterol levels in the highest quartile were 1.76 times more likely to be cognitively impaired than women in the lowest quartile. Women who lowered their LDL cholesterol levels over the four-year study were 1.64 times less likely to have cognitive impairment than women whose levels increased. Finally, women who used statins were less likely to be cognitively impaired than women who did not use statins, regardless of their LDL cholesterol levels.

To examine the association between statin use and AD risk, 912 AD patients were compared to 1669 of

their non-demented family members. After adjusting for age, sex, ethnicity, and apolipoprotein E (**apoE**) gene status, statin users were 79% less likely to have AD. Other cholesterol-lowering drugs showed a trend toward lower AD risk. In the prospective Canadian Health Study of the Aging³, 492 Canadians ≥ 65 years old who had developed dementia after baseline assessment were compared to 823 persons who had remained normal. Statin users <80 years old were 74% less likely to develop AD than non-statin users.

Statin users with AD have also been shown to have lower levels of 24S-OH-cholesterol (a reliable marker for neuronal damage in the brain)⁴ as well as lower levels of beta amyloid (**A β 42**) in the cerebrospinal fluid, which suggests that statins can retard the progression of AD pathophysiology⁵ (see “Pathophysiology of Alzheimer’s Disease” on page four).

LDL Cholesterol and AD

Elevated extracellular brain levels of LDL cholesterol (i.e. >100 mg/dL) increase AD risk by increasing A β 42 production. LDL cholesterol is initially bound within neuronal membranes by the apoE receptor, and then transferred to the LDL receptor related protein, which transports LDL cholesterol into neurons. The version of the apoE receptor produced by the $\epsilon 4$ allele tightly binds LDL cholesterol to reduce its intracellular transport⁶, which leads to increased intra-membranous and extracellular LDL cholesterol levels. These increased levels increase A β 42 production, possibly

by increasing the clipping of APP at extracellular (β -secretase) and intra-membranous (γ -secretase) sites⁷. Furthermore, A β 42 itself prevents LDL cholesterol from binding to apoE and to the LDL receptor related protein, which further increases extracellular LDL cholesterol levels and further increases A β 42 production. HDL can reduce increased A β 42 production by binding to LDL cholesterol even in the presence of A β 42⁷. This information helps explain why elevated extracellular brain levels of LDL and HDL cholesterol increase and decrease AD risk respectively, and how the ϵ 4 allele of the apoE receptor further increases AD risk.

Lowering LDL Cholesterol: Statins

The statins produce a cascade of beneficial effects over time. During the first 3-4 months, endothelial cell function is restored via nitric oxide synthetase production, and unstable atheromas are stabilized. The second event in the cascade occurs after two years of statin therapy, and involves slowing, halting or partially reversing atheromatosis in coronary and peripheral arteries, plus reduced risks of diabetes, fractures, and dementia due to AD and cerebrovascular disease. The third event in the cascade occurs after 4-5 years, and involves lowering of total and cardiac morbidity and mortality. The final event in the cascade reduces risks of hypotensive, arrhythmic and tachycardic episodes⁸.

In the next newsletter, we will discuss the role of HDL cholesterol in protecting against dementia due to AD and VD.

Reference List

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Patient Education

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the information on the next page
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Proposal for New Diagnostic Criteria for Alzheimer's Disease

The International Working Group on Diagnostic Criteria for Mild Cognitive Impairment and Alzheimer's Disease has a new proposal for new diagnostic criteria for Alzheimer's disease (AD). The proposal criteria for AD would require presence of an objective confirmed episodic memory disorder plus at least one of the following: a structural abnormality (probably atrophy of the mediotemporal lobe as seen on MRI); a characteristic biochemical marker obtained from CSF; or functional brain impairment as seen on PET or single photon emission CT. These criteria will be initially applied only to research, but will eventually be introduced as a clinical standard.

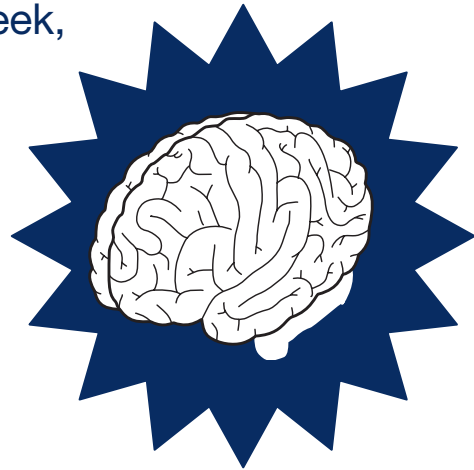
The important factor for the proposed criteria is the presence of episodic memory impairment, which must be gradual, progressive and over a period of 6 months. Episodic memory or short term memory, which can be detected by tests of delayed recall, is the first symptom of Alzheimer's disease and is manifest up to seven years before other cognitive domains are affected. Even with diagnostic support using advanced imaging technology or biomarkers, identification of memory impairment still remains the most important step in diagnosing AD.

September is Healthy Aging Month.

Maintaining a healthy brain is part of healthy aging. Following are 10 tips for keeping your mind healthy.

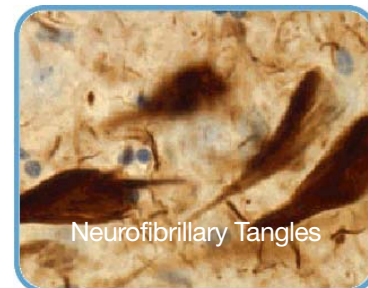
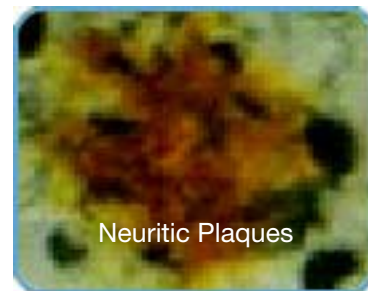
10 Tips for a Healthy Aging Brain

1. Exercise at least 3 times a week, 30 minutes each time
2. Engage in mental exercise: read, write, complete crossword puzzles
3. Eat foods high in omega-3 fatty acids: salmon, walnuts, green leafy vegetables
4. Follow a diet that's lower in calories and fat, particularly saturated fat
5. Control your cholesterol level
6. Control your blood pressure
7. Control your weight
8. Relax and sleep well
9. Manage anxiety and stress
10. Maintain a socially active lifestyle



Pathophysiology of Alzheimer's Disease (AD)

Increased neuronal production or reduced degradation and clearance of the 42 amino acid, beta amyloid (**A β 42**), is currently thought to be the predominant pathophysiological event leading to the production of AD neuropathology (A β 42 oligomers and fibrils, neuritic plaques, synapse loss and neurofibrillary tangles) and clinical expression. A β 42 production results from secretase cleavage of the β - and/or γ -secretase sites of the amyloid precursor protein (**APP**: a 700+ amino acid neuronal protein with intra- and extra-cellular domains). APP is important for synapse formation during human development and for synapse repair when any kind of brain damage occurs. Recycling of APP occurs by clipping at its α -, β -, or γ -secretase sites. Secretase clipping at the intracellular α -secretase APP site produces a fragment with no known harmful effects. Secretase clipping at the extracellular β -secretase APP site leads to further clipping at the intramembranous γ -secretase APP site to produce soluble, monomeric A β 42. Monomeric A β 42 rapidly aggregates with other A β 42 monomers to form A β 42 oligomers and fibrils, which themselves produce cognitive impairment that can be reversed with their removal¹.



A β 42 oligomers distort neuronal membrane geometry to increase calcium permeability, which triggers excessive phosphorylation of the neuron's structural proteins, called tau, and causes them to twist into paired helical filaments. Paired helical filaments block the normal flow of molecules down the branches of neurons to interfere with the maintenance of synapses, resulting in synapse loss and neuronal shrinkage. Eventually, neurons can no longer compensate and they die as a dense mass of paired helical filaments known as neurofibrillary tangles. Other pathophysiologic neuronal responses to increased A β 42 oligomers include generation of reactive oxygen species, altered signaling pathways and mitochondrial dysfunction, all of which contribute to amyloid-associated degenerative diseases and possibly other disorders associated with formation of abnormal oligomeric proteins, such as Lewy Body disease and possibly some form of Frontal-temporal lobe dementia^{2,3}.

Neurons also eject intra-membranous A β 42 oligomers, which diffuse through the extracellular space until they bind to accumulations of cellular debris called **diffuse plaques**—found in all normal aging brains. The A β 42 oligomer-diffuse plaque complex somehow triggers surrounding microglial cells to release butyrylcholinesterase, which further degrades the bound A β 42 oligomers into dense core amyloid, thus transforming them into **neuritic plaques**. As sprouting nerve fibers grow towards damaged neurons to reconnect and repair them, nearby neuritic plaques also attract these nerve fibers. If the nerve fiber grows into a neuritic plaque, it effectively creates a short circuit with no function. As neuritic plaques accumulate, so do the number of short-circuits, which interfere with the neuronal repair process and accounts for about ¼ of the functional disability associated with AD neuropathology.

To summarize, the production of A β 42 oligomers significantly contributes to all known forms of AD neuropathology.

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