DAVID S. GELDMACHER, MD
Harrison Distinguished Teaching Associate Professor,
Department of Neurology, University of Virginia Health
System, Charlottesville

Alzheimer disease prevention: Focus on cardiovascular risk, not amyloid?

■ ABSTRACT

Autosomal dominant (early-onset) Alzheimer disease and the much more common sporadic Alzheimer disease share a common pathology but not necessarily a common pathophysiology. Common cardiovascular comorbidities are associated with increased risk for Alzheimer disease and offer opportunities for intervention. Class I evidence for prevention is extremely limited. The overall body of evidence suggests the best time to intervene is in midlife, not in old age.

■ KEY POINTS

Vascular risk factors clearly increase the risk of Alzheimer disease and can be addressed. However, controlled trials in patients with hypertension or with dyslipidemia have had negative results.

Risk is lower with a diet high in antioxidants and polyunsaturated fatty acids.

Estrogen therapy has had mixed results in observational studies, mostly hinting at lower risk. However, a randomized trial of hormone replacement therapy in late life indicated a higher risk of dementia with estrogen.

Physical activity in midlife and in late life was associated with a lower risk of Alzheimer disease in observational studies. Controlled trials were not so positive, but the benefits of exercise may be slowly cumulative.

EFFORTS TO MODIFY the relentless course of Alzheimer disease have until now been based on altering the production or clearance of beta-amyloid, the protein found in plaques in the brains of patients with the disease. Results have been disappointing, possibly because our models of the disease—mostly based on the rare, inherited form—may not be applicable to the much more common sporadic form.

Ely Lilly's recent announcement that it is halting research into semagacestat, a drug designed to reduce amyloid production, only cast further doubt on viability of the amyloid hypothesis as a framework for effective treatments for Alzheimer disease.

Because of the close association of sporadic Alzheimer disease with vascular disease and type 2 diabetes mellitus, increased efforts to treat and prevent these conditions may be the best approach to reducing the incidence of Alzheimer disease.

This article will discuss current thinking of the pathophysiology of Alzheimer disease, with special attention to potential prevention and treatment strategies.

■ THE CANONICAL VIEW: AMYLOID IS THE CAUSE

The canonical view is that the toxic effects of beta-amyloid are the cause of neuronal dysfunction and loss in Alzheimer disease.

Beta-amyloid is a small peptide, 38 to 42 amino acids long, that accumulates in the extracellular plaque that characterizes Alzheimer pathology. Small amounts of extracellular beta-amyloid can be detected in the brains of elderly people who die of other causes, but the brains of people who die with severe Alzheimer disease show extensive accumulation of plaques.

Autosomal dominant vs sporadic Alzheimer disease

	AUTOSOMAL DOMINANT	SPORADIC
Age of onset	< 55 years	> 55 years
Known causative mutations	Yes	No
Inferred genetic mechanism	Amyloid overproduction	Disordered amyloid handling and clearance
Medical comorbidities	Infrequent	Common (and convey risk)

The amyloid precursor protein is cleaved by normal constitutive enzymes, leaving beta-amyloid as a fragment. The beta-amyloid forms into fibrillar aggregations, which further clump into the extracellular plaque. Plaques can occur in the normal aging process in relatively low amounts. However, in Alzheimer disease, through some unknown trigger, the immune system appears to become activated in reference to the plaque. Microglial cells—the brain's macrophages—invade the plaque and trigger a cycle of inflammation. The inflammation and its by-products cause local neuronal damage, which seems to propagate the inflammatory cycle to an even greater extent through a feed-forward loop. The damage leads to metabolic stress in the neuron and collapse of the cytoskeleton into a neurofibrillary tangle. Once the neurofibrillary tangle is forming, the neuron is probably on the path to certain death.

This pathway might be interrupted at several points, and in fact, much of the drug development world is working on possible ways to do so.

We can think of Alzheimer disease as a clinical syndrome or as a neuropathologic entity

■ GENETIC VS SPORADIC DISEASE: WHAT ARE THE KEY DIFFERENCES?

The amyloid model is based on early-onset disease, a distinct syndrome with autosomal dominant inheritance. The onset of symptoms usually occurs in the patient's 40s, but it can occur as early as the 20s or as late as the 50s. The disease is aggressive and almost always follows a 5- to 8-year course to death. In terms of its onset, course, and comorbidities, early-onset Alzheimer disease is very different than the much more common sporadic or late-onset disease found in older adults (**TABLE 1**).

Although the autosomal dominant form of the disease accounts for probably only 1% or 2% of all cases of Alzheimer disease, most animal models and hence much of the basic research and drug testing in Alzheimer disease are based on those dominant mutations. The pathology—the plaques and tangles—in Alzheimer disease in older adults is identical to that in younger adults, but the origins of the disease may not be the same. Therefore, the experimental model for one may not be relevant to the other.

In the last several years, some have questioned whether the amyloid hypothesis applies to all Alzheimer disease.[1,2] Arguments go back to at least 2002, when Bishop and Robinson in an article entitled "The amyloid hypothesis: Let sleeping dogmas lie?"[3] criticized the hypothesis and suggested that the beta-amyloid peptide appeared to be neuroprotective, not neurotoxic, in most situations. They suggested we await the outcome of antiamyloid therapeutic trials to determine whether the amyloid hypothesis truly explains the disorder.

The antiamyloid trials have now been under way for some time, and we have no definitive answer. Data from the phase II study of the monoclonal antibody agent bapineuzumab suggests there might be some small clinical impact of removing amyloid from the brain through immunotherapy mechanisms, but the benefits thus far are not robust.

■ COULD AMYLOID BE NEUROPROTECTIVE?

A pivotal question might be, "What if sick neurons made amyloid, instead of amyloid making neurons sick?" A corollary question is, "What if the effect were bidirectional?"

It is possible that in certain concentrations amyloid is neurotoxic, but in other concentrations, it actually facilitates neuronal repair, healing, and connection.

■ REDUCING METABOLIC STRESS: THE KEY TO PREVENTION?

If our current models of drug therapy are not effective against sporadic Alzheimer disease, perhaps focusing on prevention would be more fruitful.

Consider diabetes mellitus as an analogy. Its manifestations include polydipsia, polyuria, fatigue, and elevated glucose and hemoglobin A_{1c}. Its complications are cardiovascular disease, nephropathy, and retinopathy. Yet diabetes mellitus encompasses two different diseases—type 1 and type 2—with different underlying pathophysiology. We do not treat them the same way. We may be moving toward a similar view of Alzheimer disease.

Links have been hypothesized between vascular risks and dementia. Diabetes, hypertension, dyslipidemia, and obesity might lead to dementia in a process abetted by oxidative stress, endothelial dysfunction, insulin resistance, inflammation, adiposity, and subcortical vascular disease. All of these could be targets of intervention to prevent and treat dementia.[4]

Instead of a beta-amyloid trigger, let us hypothesize that metabolic stress is the initiating element of the Alzheimer cascade, which then triggers beta-amyloid overproduction or underclearance, and the immune activation damages neurons. By lessening metabolic stress or by preventing immune activation, it may, in theory, be possible to prevent neurons from entering into the terminal pathway of tangle formation and cell death.

■ LINKS BETWEEN ALZHEIMER DISEASE AND DIABETES

Rates of dementia of all causes are higher in people with diabetes. The strongest effect has been noted in vascular dementia, but Alzheimer disease was also found to be associated with diabetes.[5] The Framingham Heart Study[6] found the association between dementia and diabetes was significant only when other risk factors for Alzheimer disease were minimal: in an otherwise healthy population, diabetes alone appears to trigger the risk for dementia. But in a population with a lot of vascular comorbidities, the association between diabetes and dementia is not as clear. Perhaps the magnitude of the risk is overwhelmed by greater cerebrovascular and cardiovascular morbidity.

A systematic review[7] supported the notion that the risk of dementia is higher in people with diabetes, and even raised the issue of whether we should consider Alzheimer disease "type 3 diabetes."

Testing of the reverse hypothesis—diabetes is more common in people with Alzheimer disease—also is supportive: diabetes mellitus and even impaired fasting glucose are approximately twice as common in people with Alzheimer disease than in those without.[8] Fasting blood glucose levels increase steadily with age, but after age 65, they are higher in people with Alzheimer disease than in those without.

Glucose has some direct effects on brain metabolism that might explain the higher risk. Chronic hyperglycemia is associated with excessive production of free radicals, which leads to reactive oxygen species. These are toxic to neuronal membranes as well as to mitochondria, where many of the reactive oxygen species are generated. Free radicals also facilitate the inflammatory response.

We also see greater neuronal and mitochondrial calcium influx in the presence of hyperglycemia. The excess calcium interferes with mitochondrial metabolism and may trigger the cascade of apoptosis when it reaches critical levels in neurons.

Chronic hyperglycemia is also associated with increased advanced glycation end-products. These are toxic molecules produced by the persistent exposure of proteins to high sugar levels and may be facilitated by the presence of reactive oxygen species that catalyze the reactions between the sugars and the peptides. Glycation end-products are commonly recognized as the same as those occurring during browning of meat (the Maillard reaction).

Hyperglycemia also potentiates neuronal damage from ischemia. Animal experiments show that brain infarction in the presence of hyperglycemia results in worse damage than

Early-onset Alzheimer disease is very different in its onset and course from late-onset disease

the same degree of ischemia in the absence of hyperglycemia. Hyperglycemia may exaggerate other blows to neuronal function such as those from small strokes or microvascular ischemia.

■ AN ALTERNATIVE TO THE AMYLOID HYPOTHESIS: THE 'MITOCHONDRIAL CASCADE HYPOTHESIS'

Swerdlow and Khan[9] have proposed an alternative to the amyloid hypothesis as the cause of Alzheimer disease, known as the "mitochondrial cascade hypothesis." According to this model, as we age we accumulate more wear-and-tear from oxidative mitochondrial damage, especially the accumulation of toxins leading to reduced cell metabolic activity. This triggers the "3-R response":

Reset. When toxins alter cell metabolism, neurons try to repair themselves by manufacturing beta-amyloid, which is a "repair-and-reset" synaptic signaling molecule that reduces energy production. Under the lower energy state, beta-pleated sheets develop from beta-amyloid, which aggregate and form amyloid plaque.

Remove. Many cells undergo programmed death when faced with oxidative stress. The first step in neuronal loss is reduced synaptic connections and, hence, losses in neuronal communication. This results in impaired cognition.

Replace. Some cells that are faced with metabolic stress re-enter the cell cycle by undergoing cell division. Neurons, however, are terminally postmitotic and die if they try to divide: by synthesizing cell division proteins, duplicating chromosomes, and reorganizing the complex internal structure, the cell cannot work properly and cell division fails. In the mitochondrial cascade hypothesis, neurofibrillary tangles result from this attempted remodeling of the cytoskeletal filaments, furthering neuronal dysfunction.

■ ALZHEIMER DISEASE AND STROKE: MORE ALIKE THAN WE THOUGHT?

Although historically clinicians and researchers have tried to distinguish between Al-zheimer disease and vascular dementia, growing evidence indicates that the two disorders overlap significantly and that the pathologies may be synergistic.

Alzheimer disease has been hypothesized as being a vascular disorder.[10] It shares many of the risk factors of vascular disease, and preclinical detection of Alzheimer disease is possible from measurements of regional cerebral perfusion. Cerebrovascular and neurodegenerative pathology are parallel in Alzheimer disease and vascular disease.

Pure Alzheimer disease and vascular disease are two ends of a pathologic continuum.[11] At one end is "pure" Alzheimer disease, in which patients die only with histologic findings of plaques and neurofibrillary tangles. This form may occur only in patients with the autosomal dominant early-onset form. At the other end of the spectrum are people who have serious vascular disease, multiple strokes, and microvascular ischemia and who die demented but with no evidence of the plaques and tangles of Alzheimer disease.

Between these poles is a spectrum of overlapping pathology that is either Alzheimer disease-dominant or vascular disease-dominant, with varying degrees of amyloid plaque and evidence of microvascular infarcts. Cerebral amyloid angiopathy (the accumulation of beta-amyloid in the wall of arteries in the brain) bridges the syndromes.[12] In some drug studies that attempted removing amyloid from the brain, vascular permeability was altered, resulting in brain edema.

Along the same lines as Kalaria's model,[11] Snowden et al[13] found at autopsy of aged Catholic nuns that for some the accumulation of Alzheimer pathology alone was insufficient to cause dementia, but dementia was nearly universal in nuns with the same burden of Alzheimer pathology commingled with vascular pathology.

■ DOES INFLAMMATION PLAY A ROLE?

The inflammatory state is a recognized risk factor for Alzheimer disease, but the clinical data are mixed. Epidemiologic evidence is strong: patients who regularly take nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids for chronic, systemic inflammatory diseases (eg,

Pure Alzheimer disease and vascular disease are two ends of a continuum

arthritis) have a 45% to 60% reduced risk for Alzheimer disease.[14,15]

However, multiple clinical trials in patients with Alzheimer disease have failed to show a benefit of taking anti-inflammatory drugs. One preliminary report suggested that indomethacin (Indocin) might offer benefit, but because of gastrointestinal side effects its usefulness in an elderly population is limited.

Diabetes and inflammation are also closely linked: hyperinsulinemia is proinflammatory, promoting the formation of reactive oxygen species, inhibiting the degradation of oxidized proteins, and increasing the risk for lipid peroxidation. Insulin acts synergistically with endotoxins to raise inflammatory markers, eg, proinflammatory cytokines and C-reactive protein.[16]

It is possible that anti-inflammatory drugs may not work in Alzheimer disease because inflammation in the brain is mediated more by microglial cells than by prostaglandin pathways. In Alzheimer disease, inflammation is mediated by activated microglial cells, which invade plaques with their processes; these are not evident in the diffuse beta-amyloid-rich plaques seen in typical aging. The trigger for their activation is unclear, but the activated microglial cells and the invasion of plaques are seen in transgenic mouse models of Alzheimer disease, and activation is seen when beta-amyloid is injected into the brain of a healthy mouse.[17]

Activated microglial cells enlarge and their metabolic rate increases, with a surge in the production of proteins and other protein-mediated inflammatory markers such as alpha-antichymotrypsin, alpha-antitrypsin, serum amyloid P, C-reactive protein, nitric oxide, and proinflammatory cytokines. It is unlikely that it is healthy for cells to be exposed to these inflammatory products. Some of the cytokines are now targets of drug development for Alzheimer disease, and agents targeting these pathways have already been developed for connective tissue diseases.

In a controversial pilot study, Tobinick et al[18] studied the use of etanercept (Enbrel), an inhibitor of tumor necrosis factor-alpha (an inflammatory cytokine). They injected etanercept weekly into the spinal canal in 15 patients with mild to severe Alzheimer disease,

for 6 months. Patients improved in the Mini-Mental State Examination by more than two points during the study. Patent issues surrounding use of this drug in Alzheimer disease may delay further trials.

Thiazolidinediones block microglial cell activation

The reactive microglial phenotype can be prevented in cell culture by peroxisome proliferator-activated receptor (PPAR) gamma agonists. These include the antidiabetic thiazolidinediones such as pioglitazone (Actos), troglitazone (Rezulin), and rosiglitazone (Avandia), and indomethacin and other NSAIDs.

Using a Veterans Administration database of more than 142,000 patients, Miller et al[19] retrospectively found that patients who took a thiazolidinedione for diabetes had a 20% lower risk of developing Alzheimer disease compared with users of insulin or metformin (Glucophage).

However, rosiglitazone showed no benefit against Alzheimer disease in a large clinical trial,[20] but this may be because it is rapidly cleared from the brain. Pioglitazone is not actively exported from the brain, so it may be a better candidate, but pharmaceutical industry interest in this agent is low because its patent will soon expire.

Fish oil is another PPAR-gamma agonist, and some studies indicate that eating fish may protect against developing Alzheimer disease; it may also be therapeutic if the disease is present. Double-blind controlled studies have not been carried out and likely will not because of patent issues: the costs of such studies are high, and the potential payback is low.

◼ ESTROGEN: PROTECTIVE OR NOT?

Whether taking estrogen is a risk factor or is protective has not yet been determined. Estrogen directly affects neurons. It increases the number of dendritic spines, which are associated with improved memory. Meta-analyses suggest that hormone replacement therapy reduces the risk of dementia by about one-third.[21,22] Both positive and negative prospective studies exist, but all are complicated by serious methodologic flaws.[23,24]

The inflammatory state is a recognized risk factor for Alzheimer disease, but the therapeutic data are mixed

Combined analysis of about 7,500 women from two double-blind, randomized, placebo-controlled trials of the Women's Health Initiative Memory Study found that the risks of dementia and mild cognitive impairment were increased by hormone replacement therapy. The hazard ratio for dementia was found to be 1.76 (*P* < .005), amounting to 23 new cases of dementia per 10,000 prescriptions annually.[25]

Patient selection may account for the conflicting results in different studies. Epidemiologic studies consisted mostly of newly postmenopausal women and those who were being treated for symptoms of vasomotor instability. In contrast, the Women's Health Initiative enrolled only women older than 65 and excluded women with vasomotor instability. Other studies indicate that the greatest cognitive improvements with hormone therapies are seen in women with vasomotor symptoms.

■ WHICH RISK FACTORS CAN WE CONTROL?

In summary, some of the risk factors for Alzheimer disease can be modified if we do the following.

Aggressively manage diabetes and cardiovascular disease. Vascular risk factors significantly increase dementia risk, providing good targets for prevention: clinicians should aggressively help their patients control diabetes, hypertension, and hyperlipidemia.[26] However, aggressive control of hypertension in a patient with already-existing dementia may exacerbate the condition, so caution is warranted.

Optimize diet. Dietary measures include high intake of antioxidants (which are especially high in brightly colored and tart-flavored fruits and vegetables) and polyunsaturated fats.[26] Eating a Mediterranean-type diet that includes a high intake of cold-water ocean fish is recommended. Fish should not be fried: the high temperatures may destroy the omega-3 fatty acids, and the high fat content may inhibit their absorption.

Weigh the risks and benefits of estrogen. Although estrogen replacement therapy for postmenopausal women has had mixed results for controlling dementia, it appears to be clinically indicated to control vasomotor symptoms and likely does not increase the risk of dementia for newly menopausal women. Risks and benefits should be carefully weighed for each patient.

Optimize exercise. People who are physically active in midlife have a lower risk of Alzheimer disease.[27] Those who adopt new physical activity late in life may also gain some protective or restorative benefit.[28]

Many measures, such as taking anti-inflammatory or antihypertensive drugs, probably have a very small incremental benefit over time, so it is difficult to measure significant effects during the course of a typical clinical trial.

Clinicians are already recommending actions to reduce the risk of dementia by focusing on lowering cardiovascular risk. Hopefully, as these actions become more commonly practiced as lifelong habits in those reaching the age of risk for Alzheimer disease, we will see a reduced incidence of that devastating and much-feared illness. ■

■ REFERENCES

1. **Castellani RJ, Lee HG, Zhu X, Nunomura A, Perry G, Smith MA**. Neuropathology of Alzheimer disease: pathognomic but not pathogenic. Acta Neuropathol 2006; 111:503–509.
2. **Geldmacher DS**. Alzheimer's pathogenesis: are we barking up the wrong tree? Pract Neurol 2006(4):14–15.
3. **Bishop GM, Robinson SR**. The amyloid hypothesis: let sleeping dogmas lie? Neurobiol Aging 2002; 23:1101–1105.
4. **Middleton LE, Yaffe K**. Promising strategies for the prevention of dementia. Arch Neurol 2009; 66:1210–1215.
5. **Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM**. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996; 39:1392–1397.
6. **Akomolafe A, Beiser A, Meigs JB, et al**. Diabetes mellitus and risks of developing Alzheimer disease: results from the Framingham Study. Arch Neurol 2006; 63:1551–1555.
7. **Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P**. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006; 5:64–74.
8. **Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC**. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 2004; 53:474–481.
9. **Swerdlow RH, Khan SM**. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. Med Hypotheses 2004; 63:8–20.
10. **de la Torre JC**. Vascular basis of Alzheimer's pathogenesis. Ann NY Acad Sci 2002; 977:196–215.
11. **Kalaria R**. Similarities between Alzheimer's disease and vascular dementia. J Neurol Sci 2002; 203–204:29–34.
12. **Prada CM, Garcia-Alloza M, Betensky RA, et al**. Antibody-mediated clearance of amyloid-beta peptide from cerebral amyloid angiopathy revealed by quantitative in vivo imaging. J Neurosci 2007; 27:1973–1980.
13. **Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR**. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA

1997; 277:813–817.

14. **McGeer PL, Schulzer M, McGeer EG**. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 1996; 47:425–432.

15. **Stewart WF, Kawas C, Corrada M, Metter EJ**. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997; 48:626–632.

16. **Craft S, Watson GS**. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004; 3:169–178.

17. **Bamberger ME, Landreth GE**. Inflammation, apoptosis, and Alzheimer's disease. Neuroscientist 2002; 8:276–283.

18. **Tobinick E, Gross H, Weinberger A, Cohen H**. TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. MedGenMed 2006; 8:25.

19. **Miller DR, Fincke BG, Davidson JE, Weil JG**. Thiazolidinedione use may forestall progression of Alzheimer's disease in diabetes patients. Alzheimer's & Dementia: Journal of the Alzheimer's Association 2006 (2 suppl July):S148.

20. **Gold M, Alderton C, Zvartau-Hind M, et al**. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord 2010; 30:131–146.

21. **Yaffe K, Sawaya G, Lieberburg I, Grady D**. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998; 279:688–695.

22. **Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD**. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002; 288:872–881.

23. **LeBlanc ES, Janowsky J, Chan BK, Nelson HD**. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001; 285:1489–1499.

24. **Hogervorst E, Williams J, Budge M, Riedel W, Jolles J**. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 2000; 101:485–512.

25. **Shumaker SA, Legault C, Kuller L, et al; Women's Health Initiative Memory Study**. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291:2947–2958.

26. **Middleton LE, Yaffe K**. Promising strategies for the prevention of dementia. Arch Neurol 2009; 66:1210–1215.

27. **Etgen T, Sander D, Huntgeburth U, Poppert H, Förstl H, Bickel H**. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Arch Intern Med 2010; 170:186–193.

28. **Heyn P, Abreu BC, Ottenbacher KJ**. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 2004; 85:1694–1704.

ADDRESS: *David S. Geldmacher, MD, Department of Neurology, University of Virginia Health Systems, Charlottesville, VA; e-mail Dsg8n@virginia.edu.*