Prevention and Treatment of Alzheimer's Disease with Natural Therapeutics

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Introduction

Alzheimer's disease is the most common form of dementia in the elderly. This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. It is also one of the best known and important of all degenerative diseases. It is a condition that is associated with considerable psychological and emotional distress for patients and their families. It also represents a large economic burden for those afflicted and their families because of the long-term care that is associated with the condition. Alzheimer's disease is caused by changes in the cerebral cortex, basal forebrain, and other areas of the brain. The nerve cells that are particularly affected are those that are stimulated by the neurotransmitter called acetylcholine. The brain tissue of Alzheimer's patients is marked by moderate-to-severe changes that involve characteristic plaques and tangles. These plaques and tangles can be thought of as 'scars' caused by protein and cellular deposits. The peak incidence of the initial development of Alzheimer's disease is in individuals between the ages of 65 and 74 years. It is estimated that 3.5% of the population in the United States between the ages of 65 and 74 years of age is in at least the initial stage of Alzheimer's disease. Most individuals who have advanced disease are 85 years of age and older. Females are slightly more likely than males to develop Alzheimer's disease. Individuals with Down's syndrome are more likely to develop Alzheimer's disease than the general population. Alzheimer's disease attacks every socioeconomic and ethnic group.

Risk Factors

The cause of Alzheimer's disease is being investigated in a number of areas. Already, several genes have been linked to the development of Alzheimer's. While genetic factors may increase the likelihood that a person will develop Alzheimer's, environmental factors are believed to have an important role as well. Researchers have found a number of environmental factors that have been associated with the development of Alzheimer's, including long-term exposure to silicon or aluminum[1], chronic exposure to other toxins, free-radical damage,[2] and traumatic head injury. Like many other chronic degenerative diseases, Alzheimer's appears to be caused to a large degree by oxidative damage.[3] There is mounting evidence that antioxidant factors may help prevent or delay the onset of the disease. Researchers have also focused considerable attention on the significant amounts of aluminum that have been found in the affected areas of the brain. There is still no conclusive evidence that aluminum is the cause of the condition or that it accumulates in particular areas as a response to the condition. Some circumstantial evidence has linked chronic exposure to aluminum with the development of Alzheimer's disease.[4] Alzheimer's patients have significantly higher levels of aluminum in their brains than healthy individuals or those with dementia caused by alcohol abuse, stroke, or atherosclerosis.[5] Aluminum emanates from a variety of sources including deodorants, antacids, water supplies, and food. The most significant of these sources is likely the water supply. Aluminum compounds are used in many municipal water supplies as a means to purify the water from microorganisms. Unfortunately, these aluminum compounds in water supplies are readily absorbable by humans. It should be noted that several beverages and foods may increase the amount of aluminum that is absorbed. Coffee does not contain aluminum, but it causes increased acidity in the stomach that increases aluminum absorption by the body. Some types of tea, such as that brewed from Assan, Ceylon, and Darjeeling leaves, actually have aluminum. The acidity of tomatoes also increases aluminum absorption. Individuals should also discontinue using aluminum cookware because of the possibility of aluminum transfer into the food. Hydrogenated or partially hydrogenated vegetable oils that are commonly used in margarine and other processed foods increase the permeability of the membranes of cells, which can lead to increased aluminum absorption. Another way to reduce aluminum exposure is to buy fresh or frozen foods instead of canned goods. Antiperspirants, antacids, and toothpaste can be found that do not contain aluminum in the product or in the packaging.

High levels of exposure to mercury and silver have also been associated with the development of Alzheimer's disease. In particular, individuals with silver mercury fillings were found to be at increased risk for developing the disease.[6] It is well established that individuals with these fillings do

have higher serum levels of silver and mercury, and high levels of these elements have been associated with the development of Alzheimer's.

A study found that 17 of 19 patients with Alzheimer's disease were infected with Chlamydia bacteria.[7] A different study found that individuals with a genetic marker called the ApoE-e4 allele are at increased risk for developing Alzheimer's disease.[8] This risk is increased if the individual eats a high-fat diet during early and mid-adulthood.[9] Several studies have found evidence that Alzheimer's disease is a disease that is caused by or is a result of decreased metabolic activity in the brain.[10] It has been speculated that ApoE-e4 may be involved in the development of decreased metabolic activity that is associated with Alzheimer's.

The risk of developing Alzheimer's disease is increased in first-degree relatives of affected individuals. Researchers have identified three different variations in genes that are associated with an increased risk of developing Alzheimer's disease. The precise cause of Alzheimer's disease is unknown. The prevalent notion is that most cases of Alzheimer's disease are caused by a combination of risk factors that include age, head injury, and the lipoprotein E-epsilon 4 genotype, among several risk factors that appear to trigger pathophysiologic processes that, over time, lead to dementia.

The familial types of Alzheimer's are associated with less than 7% of all cases of Alzheimer's disease. Most cases are classified as being sporadic (ie, not inherited). Researchers have proposed that genetic mutations may alter the mechanisms by which amyloid proteins in the brain are processed. These changes in amyloid proteins and their deposition in the brain are believed to produce neurotoxic properties that lead to a variety of processes that result in the death of neurons, synapse (connections between neurons) loss, and other destructive activities.

Researchers have found an association between the presence of abnormal fingerprint patterns and the risk of developing Alzheimer's disease. These fingerprint patterns are characterized by a greater number of ulnar loops on the fingertips and a decreased number of whorls, arches, and radial loops. An absolute diagnosis of Alzheimer's disease can only be made using a careful biopsy on the brain after death.

Signs and Symptoms

The patient generally visits the physician at the behest of his family. The family typically notices a pattern of changed behaviors that can include memory problems, insomnia, anxiety, depression, disruptive behavior, and hallucinations. Memory impairment is the hallmark symptom of Alzheimer's disease and usually involves behaviors such as forgotten appointments, disorientation away from home, misplaced items, and repetitive questions. The memory impairment of Alzheimer's patients is defined as the reduced ability to learn new information and to recall previously learned information.

Alzheimer's disease has been classified into three stages. Stage One usually lasts two to four years. It involves confusion, forgetfulness, disorientation, recent memory loss, and mood changes. Stage Two often lasts two to ten years. It typically is characterized by decreased memory functioning, reduced attention span, hallucinations, wandering, restlessness, muscle spasms, reduced ability to perform logic, increased irritability, and an increased inability to organize thoughts. Stage Three generally lasts one to three years. This period most often involves the increased inability to recognize family members, a progressive inability to recognize their own image in the mirror, weight loss, incontinence, swallowing difficulty, the development of skin infections, and seizures.

Diagnosis

The diagnosis of Alzheimer's disease is based on the presence of confirmed memory impairment and the presence of one or more of the following three cognitive deficits: 1.) apraxia (impaired ability to carry out certain motor activities), 2.) aphasia (language impairment), 3.) agnosia (failure to recognize or identify objects in the environment), and 4.) impairment in executive functioning (the ability to plan, organize, sequence, and abstract). Physicians need to confirm that these deficits are not caused by other central nervous system conditions such as Parkinson's disease, cerebrovascular disease, brain tumor, Huntington's disease, or others. The health care practitioner also needs to rule out systemic conditions that can cause other forms of dementia, such as HIV. Patients in the initial stages of Alzheimer's will often make mistakes in the recall of items in a simple memory

task. These patients will also have difficulty sketching a clock with a given time. A physician might order a lumbar puncture if a chronic central nervous system infection is suspected. Standard laboratory tests in patients presenting with suspected Alzheimer's include complete blood cells counts, serum electrolyte levels, glucose levels, kidney function tests, liver tests, thyroid tests, HIV test, syphilis test, and a serum vitamin B12 test. A computed tomography scan or magnetic resonance imaging may also be performed to rule out mass lesions, hydrocephalus, and to confirm the presence of the atrophy of brain tissue associated with Alzheimer's. Some physicians will also order a hair mineral analysis to evaluate the levels of heavy metals. A hair mineral analysis can detect heavy metal intoxication, such as silver, mercury, or aluminum. The electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's. Those with the disease have a diffuse and symmetrical slowing of the brain waves that register on the EEG.

Conventional Therapy

There is a considerable amount of drug research that is currently taking place to discover effective therapeutic regimens for Alzheimer's disease. Donepezil is a drug that increases the level of acetylcholine in the brain. Research indicates that it may help improve cognition and overall brain function in patients with mild-to-moderate disease. However, the drug is extremely expensive and may not provide sufficient benefits to be cost-effective. The drug can also cause depression, abnormal dreams, anorexia, nausea, and frequent urination. Naloxone is another drug that has been prescribed for Alzheimer's disease. This drug was originally developed as an antidote for narcotic overdose. It has demonstrated some beneficial effects in Alzheimer's patients but can cause side effects such as seizures, high blood pressure, pulmonary edema, and cardiac arrhythmias. Rivastigmine is another drug that has been used for Alzheimer's patients. It also helps increase acetylcholine concentrations in the brain. This drug was recently approved by the FDA for the treatment of mild-to-moderate dementia in Alzheimer's patients. Selegiline was originally developed as a treatment for Parkinson's disease but is sometimes used in Alzheimer's patients. A host of adverse effects are associated with the use of selegiline, such as anxiety, apathy, dizziness, cardiac arrhythmias, angina, abdominal pain, asthma, hair loss, high blood pressure, and headache, among others. Tacrine is another drug that acts to increase the concentration of acetylcholine in the brain. It is used in patients with mild-to-moderate dementia. Recent studies found that tacrine is effective in improving some of the symptoms of Alzheimer's patients, but only about one-third of these patients actually respond. Patients taking tacrine need to have liver monitoring on a weekly basis because of its potential to damage the liver. Other side effects include agitation, abnormal thinking, confusion, chills, anorexia, diarrhea, nausea, indigestion, fever, and asthma, among others.

Epidemiological studies have shown an association between the use of estrogen replacement therapy in postmenopausal women and a decreased risk of developing Alzheimer's.[11] At least twelve population-based studies found that postmenopausal women who were taking estrogen hormone replacement therapy had lower rates of Alzheimer's disease than those who did not use such therapy.[12] These studies may have been flawed in that women who began estrogen therapy were in better health at the beginning of the therapy than those who did not receive the therapy.[13] Estrogen therapy may help prevent Alzheimer's disease because of its antioxidant activity. Estrogen therapy has been shown to increase the risk of developing breast cancer. A safer approach to prevent or slow the progression of Alzheimer's would be to use natural antioxidant therapy.

There is evidence that nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can reduce the risk of developing Alzheimer's disease. Researchers at Johns Hopkins University found that the use of NSAIDs such as ibuprofen reduce the risk of developing Alzheimer's disease by 30 to 60 percent.[14] Several epidemiologic studies have found that a long-term use of NSAIDs, including aspirin, can decrease the inflammatory activities that are important in the development of Alzheimer's disease.[15] Such long-term use is ill-advised, however. Long-term use of NSAIDs has been associated with a range of side effects that especially affect the gastrointestinal system.

Much of the current research using conventional therapies for AD has been centered on the drug

called memantine (Namenda). Memantine is in a class of drugs known as NMDA receptor antagonists. The underlying theory is that memantine reduces activity surrounding the NMDA receptors. Overstimulation of these receptors by glutamate has been found in many AD patients, and memantine blocks the ability of glutamate to bind with the NMDA receptors. Memantine is currently prescribed in patients with moderate-to-severe AD and is the only approved drug for patients with moderate-to-severe disease. There is some evidence that memantine can reverse memory loss in some patients and can help some patients maintain more normal levels of activities of daily living. However, there is no evidence that memantine actually slows down or reduces the progression of AD. In addition, memantine use has been associated with some side effects, such as mental confusion, constipation, dizziness, and headache.

Alternative approaches to AD Prevention

There is increasing evidence that lifestyle, including a diet rich in anti-inflammatory, and antioxidant and neuroprotective agents may reduce the risk of developing Alzheimer's. The Mediterranean diet, known primarily as a way to protect against heart disease, may reduce the incidence of Alzheimer's disease. This diet, along with others, may help prevent the development of Alzheimer's disease by possibly scavenging reactive oxygen species, strengthening the ability of neurons to protect themselves, and downregulating factors in the immune system called cytokines.

The Alzheimer's Prevention Foundation International has created a guideline of four pillars of prevention for Alzheimer's disease. The first pillar is a regimen of diet and vitamins. The diet consists of 20% of calories from "good fats", such as olive oil, flaxseed oil, and avocados. Also, 40% of calories would come from lean proteins, such as fish, soy, and turkey. The remaining 40% of calories would come from complex carbohydrates, such as legumes, fruits, whole grains, and fresh vegetables. Finally, foods with special positive effects on the brain, such as seaweed, spinach, and blueberries, would be ingested on a regular basis.

The second pillar in these guidelines involves the proper management of stress. There is increasing evidence that stress may increase the risk of developing Alzheimer's disease. Hypnosis, meditation, guided imagery, deep breathing, music therapy, massage, and prayer have all been shown to significantly reduce stress. They may, in turn, decrease the risk of developing Alzheimer's disease.

The third pillar is the use of physical exercise, brain aerobics, mind/body exercises, and meditation exercises using Kundalini yoga. Finally, their recommendations include the limited and careful use of pharmaceuticals that have shown some protective and therapeutic effect on the development and progression of Alzheimer's disease. These pharmaceuticals that include rivastigmine, galantamine, donepezil, and memantine are discussed in the Conventional Therapy section of this paper. Other agents that have been shown to reduce the risk of Alzheimer's disease include non-steroidal anti-inflammatory agents, aspirin, deprenyl, and statins

Stress reduction

A lifetime study of clergy members in the Catholic Church found that those exposed to high levels of chronic psychological stress were more than twice as likely to develop Alzheimer's than those with low levels of psychological stress.[15] Cortisol is released by the adrenal glands and is a measure of the stress levels in the body. It is also known that high levels of stress negatively impact the hypothalamus, which is a center of learning and memory. A study of individuals with Alzheimer's disease found that cortisol levels were significantly higher than in healthy control subject.[16]

Diet Therapy

There is accumulating evidence that nutrition is important in the prevention and control of Alzheimer's disease. Many of the constituents of these beneficial diets are the same compounds that will be mentioned later in the Nutritional Therapy section. One of the main concerns in an Alzheimer's patient is to maintain sufficient nutrient intake and prevent malnutrition. Research indicates a diet high in carbohydrates is more appealing to the Alzheimer's patient and will lead to improved levels of food intake.[17] The key in the prevention of disease is to regularly ingest sufficient quantities of these constituents in the diet. Research has repeatedly shown that key nutrients obtained in the diet have a more powerful general

effect than supplementation with the same levels of constituents.

A study in mice found that a diet rich in the omega-3 fatty acid docosahexaenoic acid decreases the ability of the body to produce the amyloid protein, which is the key process in the development of Alzheimer's disease.[18] There is increasing evidence that calorie restriction may increase longevity in both animals and humans. Similar evidence has been found in Alzheimer's research models where a reduction in calories produces effects on brain neurons that reduce the risk of developing Alzheimer's disease.[19] The so-called Mediterranean Diet that involves the high intake of monounsaturated fats, cereals, and wine has been associated with an increased risk of cognitive decline.[20]

Nutritional Therapy

Ginkgo Biloba

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of ginkgo biloba has been found in several studies to improve the symptoms and slow the progression of Alzheimer's disease. A study of 309 patients with mild dementia was performed. The patients were given either 120 milligrams of ginkgo biloba extract or placebo every day for up to a year.[21] At the six-month point, 27 percent of those using ginkgo had moderate improvement on a variety of cognitive tests. Only 14 percent of those using placebo had an improvement on these tests. In a separate trial, 112 patients with chronic cerebral insufficiency received 120 milligrams per day of ginkgo biloba extract.[22] The researchers found that the use of this extract led to significant improvements in blood and oxygen flow. Restricted blood and oxygen flow to the brain may be an important factor in the development of Alzheimer's.

Ginkgo biloba extract (GBE) appears to be most effective in the early stages of Alzheimer's. This could potentially mean that patients with early Alzheimer's may be able to prevent being placed in a nursing home and to maintain a reasonably normal life. GBE has been shown to have the ability to normalize the acetylcholine receptors in the hippocampus area of the brain (the area most affected by the disease) in aged animals.[23] GBE has also demonstrated the ability to increase cholinergic activity and to provide improvements in other aspects of the disease.[24] A double-blind study of 216 Alzheimer's patients or dementia caused by small strokes found that 240 milligrams of GBE daily led to significant improvements in a variety of clinical parameters when compared to placebo.[25] The most effective form of GBE is one that is standardized to a concentration of 24 percent Ginkgo flavoglycosides.

A study compared the effectiveness of the most common Alzheimer's drugs, such as donepezil and rivastigmine, to that of a Ginkgo extract called EGb 761.[26] The researchers determined that EGb761 was as effective as any of these commonly-prescribed drugs in treating the symptoms of Alzheimer's patients. In general, various forms of Gingko have been found to be safe, but in individuals who take aspirin or other anticoagulant drugs, Gingko should be taken with great caution and with the advice of a physician. Ginkgo is sold as a drug and regulated in Germany, and it is used in many other parts of the world to slow the progression of various forms of dementia. EGb 761 is the most commonly sold form of Gingko in Europe.

A different study found that EGb761 prevents beta-amyloid toxicity to brain cells, a key part of the development of the disease.[27] All forms of Gingko need to be taken consistently for at least 12 weeks-a potentially difficult task for Alzheimer's patients-to determine whether the supplement is working. A recent double-blind, placebo-controlled randomized study of patients with Alzheimer's found that EGb 761 produced significant improvements in cognitive function compared to a placebo group.[28] Other recent comprehensive surveys of multiple clinical trials found similar results with EGb 761 in these patients.[29] An additional study found that EGb 761 produced cognitive improvement compared to placebo over a 26-week period using a variety of research measures.[30] This study also demonstrated that EGb 761 was as safe as placebo during the study period. A new double-blind, randomized, placebo-controlled study found that EGb 761 is as effective as donepezil in the treatment of Alzheimer's disease symptoms and is believed to be a safer alternative.[31] An additional study found that EGb 761 prevents the accumulation of amyloid beta.[32] A different study found that ginkgo biloba

was well tolerated in a group of patients with Alzheimer's dementia and stabilized cognitive function over a six-month period.[33] A meta-analysis (a mathematical analysis of multiple clinical trials) of research comparing gingko biloba with cholinesterase inhibitors, which are the mainstream pharmaceutical treatment for dementia, found that gingko biloba produced beneficial effects when compared with placebo.[34]

Vitamin E

Vitamin E is a well-known antioxidant that is a good candidate to prevent or halt the progression of the typical biological processes associated with Alzheimer's disease. A study of 341 patients with moderately severe Alzheimer's disease who received the drug selegiline, vitamin E, a combination of the two, or placebo found that patient survival was greatest in the group that received vitamin E only.[35] The vitamin E-only group also had the lowest rate of institutionalization of the patient groups. The daily doses of the various treatments were 2,000 International Units of vitamin E and 10 milligrams of selegiline. The positive effects of vitamin E would likely be greater if the therapy is begun at an earlier stage of the disease.

Newer evidence in animal studies has further confirmed the importance of vitamin E deficiency in the development of Alzheimer's.[36] A new study in humans found that vitamin E inhibits the oxidation processes that are involved in the development of amyloid beta-peptide, the key underlying process involved in the development of Alzheimer's.[37] A population-based study published in the prestigious Journal of the American Medical Association found that individuals who had a high dietary intake of vitamin E over a lifetime had a lower risk of developing Alzheimer's disease.[38] A study found that a combination of vitamin E and C supplementation produced higher levels of the two vitamins in the cerebrospinal fluid.[39] The levels of these two vitamins are low in patients with Alzheimer's disease.

A newer epidemiological study has found that vitamin E has strong effects against oxidative processes in the brain and that the combined use of vitamin E and vitamin C reduced the incidence of developing Alzheimer's disease by 64% over a lifetime.[40] A different study found that vitamin E has a protective effect in the brain by preventing damage from amyloid beta proteins that is associated with Alzheimer's disease.[41] A new study in mice has found that oxidative processes are critical in the early stages of Alzheimer's disease and that vitamin E supplementation can prevent these oxidative processes from occurring. A newer study discovered that vitamin E deficiencies are associated with the development of AD. An additional study found that vitamin E administration can prevent the oxidative stress associated with exposure to amyloid beta proteins.

Thiamine

Thiamine, along with several other B-vitamins, has a demonstrated role in a variety of cardiovascular and brain functions. In particular, thiamine produces similar effects in the brain as acetylcholine, which is the primary chemical involved in normal memory function and the lack of which is key in the development of Alzheimer's disease. In fact, thiamine mimics acetylcholine in many ways. Thiamine has been shown to increase the effects of acetylcholine.[31] A study found that the elderly are vulnerable to thiamine deficiency.[32] Two studies found that supplementation with 3 to 8 grams per days of thiamine improved mental function in patients with Alzheimer's disease and other forms of senility.[33] Administration of thiamine at these levels is generally regarded as safe. A new study has found that thiamine deficiency is associated with an increased risk of developing Alzheimer's disease.[82]

Vitamin B12

Vitamin B12 deficiencies have also been linked to Alzheimer's disease.[34] Vitamin B12 deficiencies can lead to nerve malfunction that includes numbness and pins-and-needles sensations. These sensations have been associated with Alzheimer's disease. Vitamin B12 deficiencies have also been linked with other types of impaired cognitive and neurological function in the elderly.[35] There is evidence that aluminum deposits in the brain prevent the brain from using vitamin B12. Anyone who is displaying signs of dementia should have an analysis performed to determine vitamin B12 levels. Vitamin B12 supplementation has led to improved mental function in patients with impaired mental function and a vitamin B12 deficiency.[36] As with many anti-Alzheimer's agents, early

treatment results in the best effects. Some patients who have had Alzheimer's disease for less than six months have had a complete reversal of disease when supplemented with vitamin B12 and/or folic acid.[37] Prolonged vitamin B12 deficiency may not be reversible with supplementation in some individuals. The most effective forms of vitamin B12 in the body are called methylcobalamin and adenosylcobalamin. Cyanocobalamin is the most commonly found form of vitamin B12 supplementation, but it requires additional reactions in the body to become effective. Elderly individuals may be less efficient in performing this conversion, so the other forms may be the most effective way to treat those with Alzheimer's.

A new study has found that low levels of vitamin B12 in the blood of dementia patients increased the risk of these patients developing hallucinations and sleep disturbances, which are two of the prominent complications of dementia-type diseases.[38] A study of folic acid and vitamin B12 found that a combination of the vitamins reduced levels of homocysteine in the blood of Alzheimer's patients.[39] Researchers have found that homocysteine is a key biochemical factor in the development of Alzheimer's disease. High levels of homocysteine in the blood may be a risk factor for the development of Alzheimer's. Other research has shown that Alzheimer's patients do not properly metabolize vitamin B12.[49] This research suggests vitamin B12 supplementation could slow progression or prevent some aspects of the disease. A newer study found that low levels of vitamin B12 in the blood are associated with an increased risk of developing Alzheimer's over a lifetime.[41] A newer study found that vitamin B12 deficiency in patients who already have AD are more likely to have a variety of neuropsychological disorders than those with more normal levels of vitamin B12 in the blood.[42] A different study found that vitamin B12 levels are important in the prevention of AD, but the researchers found that once AD develops, vitamin B12 supplementation is of little benefit in the control of the disease.[43]

Folic Acid

Folic acid is known to play a vital role in a variety of biological processes in the body. Folic acid deficiencies have been associated with the development of depression. A study of depressed patients found that 31 to 35 percent of the individuals were folic acid-deficient.[44] This type of depression is more common in the elderly. The correction of folic acid deficiencies in these elderly patients often results in the correction of depression.[45] Depression is also one of the most common presenting symptoms of Alzheimer's disease. A study of 96 depressed patients with dementia and folic acid deficiency found that depression was significantly reduced after only three weeks of therapy with a form of folic acid.[46] A study of nuns with Alzheimer's aged 78 to 101 years old living in a convent found that brain atrophy, as determined at autopsy, was strongly associated with low levels of foliate (the form of folic acid used by the body) in blood serum.[47] A case-control study of 164 Alzheimer's patients and healthy control subjects aged 55 years or older found that low levels of folate and vitamin B12 in the blood was associated with Alzheimer's disease.[48] However, a different study that evaluated the levels of serum folate, vitamin B12, and other factors in 52 Alzheimer's patients, 50 hospitalized controls, and 49 healthy elderly subjects found no significant differences in folate or vitamin B12 levels between the three groups.[50] A recent, population-based study found that individuals with low levels of folate in the blood were twice as likely to develop Alzheimer's compared to those with normal folate levels.[51] Newer research has found that low levels of folate in the blood are associated with an increased risk of developing AD. This effect was reinforced when homocysteine levels in the blood were increased.[52] Low folate levels are also associated with an increased risk of cognitive decline in otherwise healthy older adults who do not have AD.[53] Another study found that folate deficiencies are a risk factor for both vascular dementia and AD, and this risk is increased when increased levels of homocysteine are present.[54]

DHEA

Dehydroepiandrosterone (DHEA) is the most common hormone in the body. It is also found in large quantities in the brain. DHEA levels decrease in the blood and the brain with age and are thought by many to be associated with many of the symptoms of aging. The precise role of DHEA is unknown other than its role as a source for other steroid hormones in the body. In recent years, several studies have demonstrated an association between decreasing levels of DHEA

and the development of age-related conditions such as arthritis, heart disease, diabetes, and obesity. Two separate studies suggest DHEA can improve memory and enhance cognitive function in elderly persons with cognitive problems.[55],[56] A case-control study found that a group of 14 persons with Alzheimer's disease had significantly lower levels of DHEA sulfate in the plasma compared to 13 matched healthy controls.[57] A study of 52 patients with Alzheimer's found that those with higher plasma DHEA sulfate levels scored higher on a variety of cognitive tests than those with lower DHEA sulfate level.[58] DHEA has also been found to have the ability to protect cells from oxidative damage to the hippocampus part of the brain.[59] This is among the regions of the brain most affected by Alzheimer's disease. A randomized, double-blind, placebo-controlled study found that three months of therapy with DHEA improved cognition compared to placebo.[60] A new study of patients with AD found that the administration of DHEA sulfate combined with insulin improved a variety of physiologic factors associated with the disease.[61]

L-Acetylcarnitine

Carnitine is a supplement that has a variety of vitamin-like qualities. It is a key factor in the transport of long-chain fatty acids involved in energy metabolism in the body. In the last two decades, a particular form of carnitine, L-acetylcarnitine (LAC), has been studied extensively as a potential treatment for age-related memory problems, senile depression, and Alzheimer's disease. LAC is produced naturally in the brain and has been found to be more effective than standard carnitine in affecting brain function.[62] Chemically, LAC is very similar to acetylcholine, and that is what gave researchers the idea to use it as a supplement for depleted acetylcholine stores in Alzheimer's patients. LAC has been found to be an effective treatment for those with memory problems and depression.[63] Several controlled and rigorous studies have demonstrated that LAC can slow the progression of Alzheimer's disease.[64] One of these studies involved 130 Alzheimer's patients.[65] The researchers gave 2 grams of LAC or placebo to respective groups of patients for one year. The LAC ranked higher on all 14 cognitive measures after one year. As with other anti-Alzheimer's agents, results are best if LAC is given to the individual at an early stage of disease. LAC seems to have particularly strong effects in preserving and improving memory and constructional thinking. A one-year, multicenter, double-blind, placebo-controlled randomized study of 112 Alzheimer's patients and 117 healthy controls were given LAC.[66] At the end of the trial, Alzheimer's patients had less cognitive decline in one of the mental measures. A longitudinal, double-blind, parallel group, placebo-controlled study of 334 patients with Alzheimer's found that LAC slowed the progression of disease symptoms.[67] A study of Alzheimer's patients found that 2 grams per day of L-acetylcarnitine decreased attention deficits by 50% when it was combined with acetylcholinesterase inhibitors.[68] A new review of several studies found that dementia patients benefit in an overall sense when receiving L-acetylcarnitine over a long period of time.[69] A study has also elucidated how L-acetylcarnitine might positively affect Alzheimer's disease on a molecular level.[70]

Zinc

Zinc deficiency has been cited as a factor in the development of Alzheimer's disease.[71] Zinc is involved in a wide variety of cellular processes, particularly in the formation of enzymes critical to the replication of DNA and in the creation of proteins. There is some evidence that dementia may be caused be errors in DNA processes. Zinc is also an important factor in antioxidation processes. It is generally accepted by scientists that Alzheimer's is a disease caused by oxidation processes. Insufficient quantities of zinc in the body could be associated with the destruction of nerve cells and the formation of plaques and tangles that is associated with Alzheimer's. Investigators have found that Alzheimer's patients have decreased levels of zinc in the cerebrospinal fluid and brain compared to healthy individuals. A study of ten Alzheimer's patients who were given 27 milligrams of zinc daily found that eight patients had definite improvement in social behavior, memory performance, comprehension ability, and communication skills.[72] One of the patients had improvement in these areas that was so significant that the family and the attending medical staff described it as "unbelievable." New research indicates that zinc might have both a beneficial and a negative effect in preventing Alzheimer's disease.[73] Further research is needed to determine the proper dietary levels of zinc to prevent Alzheimer's disease.

Phosphatidylcholine

Researchers have found that phosphatidylcholine, a key substance found in lecithin, supplementation can lead to increased levels of acetylcholine in the brain. This would suggest that phosphatidylcholine would be effective in treating Alzheimer's disease. However, the actual defect in Alzheimer's disease is associated with defects in the enzyme acetylcholine transferase. This enzyme allows the combination of choline with an acetyl molecule to form acetylcholine. The addition of choline by way of phosphatidylcholine does not affect the activity of the critical enzyme, however. This lack of efficacy has been borne out in at least three studies that demonstrated inconsistent results in cognitive improvement in patients with Alzheimer's disease.[74] Some who believe that insufficiently low levels of phosphatidylcholine were used, that the patient sample sizes were too small, and that the design of these trials was generally poor has criticized this research. Despite the outcome of these studies, a patient with mild-to-moderate Alzheimer's disease may benefit from supplementation with 15 to 25 grams of a high-quality phosphatidylcholine supplement daily. If no improvements are noted after two weeks, this therapy should probably be discontinued because of the cost of this supplement and the side effects, such as nausea, that often accompany its use. A new study has provided evidence that phosphatidylcholine breaks down at a faster rate in Alzheimer's patients than in healthy persons.[75] This suggests a role for phosphatidylcholine supplementation in Alzheimer's patients. A new study found that a combination of vitamin E, pyruvate, and phosphatidylcholine provides more protection against brain oxidation processes in dementia-type diseases than vitamin E alone.[76]

Phosphatidylserine

Phosphatidylserine is a compound in the brain that is involved in the creation and protection of the integrity and fluidity of the membranes of cells. In a typically healthy individual, there is a sufficient quantity of phosphatidylserine produced in the brain to maintain the integrity of the cellular membranes. In individuals with folic acid and vitamin B12 deficiency, the brain may not be able to manufacture sufficient quantities of the compound to protect critical structures. A total of 11 double-blind studies have been performed that evaluated the effects of phosphatidylserine on patients with Alzheimer's disease, depression, or age-related cognitive impairment.[77] All of them found good outcomes in these patients after using phosphatidylserine.[78] The largest of these trials involved 494 elderly patients between the ages of 65 and 93 years with moderate-to-severe senility.[79] The researchers assessed the patients on a variety of functions including cognitive function, behavior, and mood before the therapy began and at the end of the trial. They determined that the group receiving phosphatidylserine had significant improvements in all of these measures. A study of phosphatidylserine administration in a group of elderly patients with age-related memory decline found memory improvement over a 12-week trial period.[80]

NADH

The coenzyme nicotinamide adenine dinucleotide (NADH) is a substance that is in every living cell in the body. NADH is involved in energy metabolism in the cell. Researchers have discovered that cellular activity related to NADH is decreased by some 25 to 50 percent in patients with Alzheimer's disease. An open label study in Austria involving 17 Alzheimer's patients found that patients who received 10 milligrams of NADH before breakfast every morning had a 240 percent increase in NADH cellular activity after only two weeks of therapy.[81] All of the patients, including those with the most severe forms of dementia, had significant cognitive improvement after two weeks.

Music Therapy

Several studies have demonstrated that music therapy provides beneficial effects to Alzheimer's patients. A study of 18 elderly Alzheimer's patients aged 55 to 95 years with severe disease found that music played during bath time led to significant decreases in aggressive behavior events over a two-week period.[83] A different study found that 20 male patients with the condition had significant increases in melatonin levels, a key hormone in the body associated with sleep, healing and relaxing effects, after half-hour, daily sessions of music therapy for four weeks.[84] Yet another study of Alzheimer's patients found that an individual with Alzheimer's disease had improved cognitive scores after listening to a Mozart piano sonata.[85] A twin sibling of the patient, also with Alzheimer's, had

no increase in these cognitive measures following exposure to a period of silence or popular music from the 1930s.

A new study of 10 patients with senile dementia found that music therapy helped these patients as measured by a variety of physiologic factors.[86] Another study found significant improvements in several social and emotional measures in 14 patients with Alzheimer's who received music therapy for two months.[87] A new study has found that music therapy improves autobiographical memory in AD patients.[88] A different study found that music therapy produces a variety of behavioral, stress, and immunological effects that are associated with positive memory changes in AD patients.[89]

Therapeutic Touch and Massage

There is research that suggests therapeutic benefits for Alzheimer's patients using therapeutic touch and massage. A study of four elderly Alzheimer's patients who received two, half-hour sessions for six months was performed.[90] The researchers found improvement in the patients on a variety of measures including increased physical relaxation, improved communication, increased sleepiness, and a decrease in abnormal behaviors. A different study of therapeutic touch involved 16 advanced Alzheimer's patients who received therapeutic touch therapy lasting 12.4 minutes and 11 control patients who did not receive therapy.[91] Advanced cases of Alzheimer's disease are characterized by changes in body language and behaviors indicative of discomfort in the patient. The researchers found that the therapeutic touch therapy significantly reduced discomfort in these patients in as little as five sessions. A different study found evidence of benefits when slow-stroke massage was used to decrease agitation in advanced cases of Alzheimer's.[92] A study that measured anxiety and dysfunctional behavior in Alzheimer patients found that expressive physical touch combined with visualization led to decreased anxiety and dysfunctional behavior in advanced Alzheimer patients.[93] A different study found that both therapeutic touch and hand massage reduced agitation levels in these patients.[94] This particular study found that hand massage was the more effective of the two therapies. A study of 10 patients with Alzheimer's found that the application of therapeutic touch every 20 minutes for 10 hours per day led to significant improvements in agitation.[95]

Antioxidants

As stated earlier, Alzheimer's disease is a process characterized by oxidative properties. Therefore, antioxidants, in general, should have positive effects in both the prevention and treatment of Alzheimer's. A study found that antioxidants such as vitamin A, vitamin D, lycopene, and beta-carotene were all significantly lower in Alzheimer's disease patients than controls.[96] The best studied of the remaining antioxidants is vitamin C. A study found that plasma vitamin C levels are lower in patients with Alzheimer's disease and that these levels are associated with the degree of cognitive impairment.[97] A prospective study of 633 patients aged 65 years and older found that high-dose supplementation with vitamin C decreased the risk of developing Alzheimer's disease.[98] None of the 23 high-dose vitamin C users in this study developed Alzheimer's when, statistically speaking, 3.3 would have been expected to develop the disease. A case-control study found that beta carotene levels are lower in Alzheimer's disease patients than in healthy controls.[99] A study of 38 Alzheimer's patients and 42 healthy control subjects found that beta carotene levels are lower in patients than in healthy individuals.[100] Other antioxidants such as selenium, glutamine, taurine, coenzyme Q10, pantethine, and magnesium would likely be beneficial to Alzheimer's patients but have not yet been thoroughly studied. Magnesium, for instance, is a particularly good agent to study because of its demonstrated to block the absorption of aluminum in the intestines as well as across the blood-brain barrier.

Miscellaneous Therapies

A traditional Japanese herbal therapy called Zokumei-to produced learning improvements and decreased neuron loss in mice that received the compound over a 15-day period.[101] More than one study has found that huperzine A, derived from club moss, improved cognitive function and quality of life in Alzheimer's patients.[102] A placebo-controlled trial involving patients with Alzheimer's found that 60 drops per day of the herbal compound Melissa officinalis extract produced significantly better outcomes on a variety of measures compared to placebo.[103] A traditional Chinese herbal medicine, Zhi Ling Tang, demonstrated positive effects in

32 cases of senile dementia.[104] A new population-based study of 815 persons found that those who consumed fish at least once per week were 60% less likely to develop Alzheimer's disease than those who rarely or never consumed fish.[105] A case-control study of 108 persons found that those individuals who consume significant (198 mg per day on average) levels of caffeine were significantly less likely to develop Alzheimer's disease than those who consumed significantly less caffeine (73 mg per day).[106]

A new study of acupuncture combined with music therapy found that this combination approach improved a variety of measures in AD patients.[107] Among the many established positive health effects of green tea, research is increasingly recognizing that green tea is also beneficial in AD patients.[108] Like so many effective agents in AD patients, these effects seem to be related to the ability of green tea to prevent the negative oxidative stress reactions associated with amyloid beta protein. An additional study has further validated these effects and shown that green tea can reverse the progression of disease in a mouse model.[109]

The commonly-used sleep-inducing agent melatonin has also shown some positive effects in Alzheimers disease. A new study has found that melatonin reduces the negative effects of amyloid beta proteins.[110] A different study using an animal model has found that melatonin has positive effects in AD when given early in the course of disease.[111] A different study examined the importance of sleep in the development of AD. The researchers found that poor sleep habits and the presence of sleep disorders is associated with an increased risk of developing various type of dementia, including AD.[112]

A new study has found that the progression of AD symptoms can be slowed down with social networking.[113] The researchers found that as the size of the number of social networking interactions increased, the severity of AD symptoms lessened.

The polyphenols in wine are widely recognized to have beneficial effects in the prevention and control of heart disease, but there is some new evidence that moderate wine consumption (1-2 glasses per day) may reduce the risk of AD.[114]

A different study has found that black currents, which contain anthocyanins and polyphenols, help protect signal pathways that are vital to learning and memory and, possibly, protect against Alzheimer's disease. Newer research suggests that there is a connection between diabetes-like illness and the risk of developing AD. Researchers have found that autopsied brains of AD patients have decreased levels of insulin in critical parts of their brains. This suggests that diabetes prevention may also help prevent AD.

Tea has also shown evidence that it may prevent AD. The researchers found that both green and black tea inhibited enzymes that are associated with the development of AD. A new study has found that curcumin, the dietary staple from India, inhibits the formation of beta amyloid. The researchers believe that it is the anti-inflammatory effects of curcumin that may help prevent AD.

Exercise Therapy

As mentioned earlier, exercise therapy can reduce the risk of developing AD.[115] An additional study of older subjects found that exercise reduces the risk of developing vascular dementia and AD.[116]

Resources

Alzheimer's Disease Education and Referral (ADEAR) Center
P.O. Box 8250
Silver Spring, MD 20907-8250
1-800-438-4380
www.alzheimers.org

Alzheimer's Association
225 N. Michigan Avenue, Suite 1700
1-800-272-3900
www.alz.org

National Institute on Aging Information Center
P.O. Box 8057
Gaithersburg, MD 20898-8057
1-800-222-2225
1-800-222-4225
www.nia.nih.gov

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