Omental Transposition in Treatment of Alzheimer Disease

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It is now recognized that Alzheimer disease (AD) is one of the most devastating problems confronting the practice of medicine today. This disease has severe social and economic consequences that will only increase greatly in the future. Currently, there are 1,000 new cases of AD diagnosed daily in the United States. When these patients are added to the 4.5 million Americans already diagnosed with AD, coupled with the expected arrival of future millions of “baby boomers,” many of whom will get AD, the result in costs to individuals and government will be in the multiple billions of dollars.

BACKGROUND
The neurodegenerative effects of AD have been well-established, but, because the exact cause of AD remains unknown, it is difficult to develop programs to prevent and treat the disease with any degree of precision. What is known is that in the brain of a patient with AD, there are, at any one time, three neuronal states: normally functioning neurons, dead neurons, and neurons that are slowly deteriorating. The goal in prevention and treatment of AD will be to maintain the viability of normal cerebral neurons and improve neuronal function, or at least prevent it from deteriorating.

AD is a disease in which neurons die slowly during the course of many years. The dementia that eventually occurs as a hallmark of the disease begins to manifest itself when there is loss in the critical mass of neurons located in key regions of the brain that are responsible for cognitive function. When these critically located cerebral neurons lose function during the course of time, dementia can eventually result.

ETIOLOGIC CONCEPTS

Amyloid hypothesis
There is a belief among many researchers that a relationship exists between the presence of amyloid plaques within the brain and development of AD. Because the major component of an amyloid plaque is amyloid-β protein (Aβ), this has led to the belief that the amyloid deposition within these plaques is responsible for development of AD. This hypothesis might, at first glance, appear reasonable, but let us examine some of the features of this concept that make its believability unsettling:

1. Presence of amyloid in Petri-dish preparations can cause destruction of neurons; but there is no evidence that amyloid present in the human brain has ever been found to be neurotoxic.
2. There appears to be no relationship between the number of amyloid plaques in the human brain and the degree of dementia severity seen in AD patients.
3. It has been shown that transgenic mice can produce Aβ deposits in association with cognitive loss. It should be stressed that cognitive loss in these rodents occurs before the Aβ deposits that eventually develop within the brain.
4. Many individuals who exhibit normal cognition before their death are found at autopsy to have abundant numbers of amyloid plaques in their brain, some with numbers comparable with patients with AD dementia.
5. Braak and Braak, in their publications, demonstrated that the earliest neuropathological indication of AD is not the number of senile plaques present in the brain.

Despite increasing evidence that amyloid plaques are not the underlying cause of AD, enthusiasm continues to persist that they are the cause of the disease. To lessen the probability that amyloid plaques are detrimental to the brain and are the basis for AD, a recent publication has suggested that amyloid–beta peptide are actually beneficial to neuronal survival.

Cholinergic hypothesis
There remains a belief that cerebral cholinergic deficiency might be the cause of cognitive loss in AD patients. This is the basis for the continuing and widespread use of cholinesterase inhibitors in AD, which are administered in an attempt to maintain sufficient levels of acetylcholine (ACh) within the brain. These agents apparently create their effect by impeding the enzyme cholinesterase from breaking down ACh, which is the neurotransmitter that is essential, but considered deficient, in producing adequate cholinergic transmission in critical areas of the brain involved.
with cognition and memory. Because cholinesterase inhibitors have been shown to exert modest but temporary improvement in AD patients, possibly because of a limited increase in cerebral blood flow (CBF), the belief persists that a lowered ACh level in AD might well be the main cause of the disease, and if ACh could be increased, especially in the hippocampal area, the AD patient would benefit. This concept warrants questioning.

Choline acetyltransferase (ChAT) is an enzyme involved in the synthesis of ACh and serves as a specific marker for cholinergic neurons. If a lower level of ACh might be the basis for AD, one would expect concentrations of ChAT to be depressed in AD patients as compared with normal controls. Recent studies of patients with mild cognitive impairment (MCI) and moderate AD found that ChAT levels were no different than levels found in nondemented aging patients. It was also found that ChAT levels were elevated in the frontal cortex and hippocampus in patients with MCI. ChAT levels were found to be reduced only in patients who were at the end stage of their disease. These findings lessen the support that ACh is the underlying cause of Alzheimer’s disease.

Cerebral hypoperfusion

It has been well-established that there is a decrease in CBF in AD. It has also been generally accepted over the years that the reason for the decrease in CBF in AD patients is neuronal degeneration, which decreases the need for CBF. There is now increasing information that suggests that AD is not the result of neurodegeneration causing the decrease in CBF, but it is mainly the decrease in CBF, especially during advanced aging, that leads to neurodegeneration in AD.

If AD is a result of diminished CBF, there are many conditions that lead to a lowering of CBF, the most important of these is aging, which is a normal phenomenon that occurs in all individuals. In addition to aging as a risk factor for AD, there are many other conditions closely associated with development of AD that have a negative effect maintaining CBF. These risk factors include hypertension, coronary artery disease, cardiac arrhythmias, head trauma, myocardial infarction, arteriosclerosis, hypercholesterolemia, diabetes type 2, smoking, obesity, and others.

A lowering of CBF leads to inadequate oxygen, glucose, and other biologic substances presented to the brain, which are crucial for neuronal survival. Presence of these biologic agents is especially critical for survival of key neurons that are involved in development of AD. When these specific neurons are chronically deprived of the nutrients that are necessary for their continued survival, a serious disruption occurs in the intracellular energy system within the neuron. The effect of this intraneuronal disruption severely impacts the mitochondrial apparatus within the cell that is directly involved in production of adenosine triphosphate (ATP), which is the energy source of a cell. When sufficient numbers of critically located neurons are affected by this loss of neuronal energy, the end result is dementia of the AD type.

Dependency on blood flow required for ATP production becomes highly critical if ATP deficiency occurs in neurons located in crucial areas of the brain, such as the hippocampus. When these neurons are deprived of their energy source (ATP) because of decreased CBF, oxidative and endoplasmic stress occurs, which directly affects the intracellular mitochondria that is essential for subsequent production of ATP. Oxidative stress arising in the mitochondria has an unfavorable effect on the endoplasmic reticulum and other locations within neurons, which has a negative effect on intracellular protein metabolism, resulting in intracellular-extracellular β amyloid peptide accumulation. These findings add credibility to the idea that Aβ production is not the cause of neuronal death in AD, but is a marker indicating cellular injury within a neuron, resulting in decreasing ATP levels caused by a decrease in CBF.

Recent studies have shown the closely associated relationship of decreased CBF and development of AD. Phase-contrast MRI was used to measure total CBF flowing to the human brain by calculating the blood volume that passes through the internal carotid and basilar arteries. This study demonstrated a significant decrease in the volume of blood flow that passed through these arteries in AD patients (a mean blood flow of 442 mL/minute) as compared with a mean blood flow of 551 mL/minute in nondemented age-matched subjects (p < 0.001). In a younger age group of normal subjects (median age 29 years), phase-contrast MRI studies showed a substantially higher mean blood flow rate of 742 mL/minute, which passed through their internal carotid and basilar arteries. This study demonstrated the marked decrease in the blood supply that normally flows to the brain of elderly and AD patients in
comparison with young individuals. The concept that a decreased CBF level can lead to neuronal death and eventual AD has been present for more than a decade, having been raised by de la Torre in 1993.\textsuperscript{20} A more recent article stated simply that “chronic or transient suboptimal brain perfusion can well contribute to the metabolic perturbations that are responsible for the lesions characteristic of AD.”\textsuperscript{21}

A more recent study (Rotterdam) also showed that CBF velocity was an additional factor implicated in AD development, based on the evaluation of “several thousand demented and nondemented elderly patients.”\textsuperscript{22} This combination of decreased CBF and diminished CBF velocity would have a negative effect on ischemic-sensitive neurons located in critical areas of the brain, such as the hippocampus. As the volume of blood and its velocity continues to diminish to the brain, widespread neuronal deterioration would be expected to eventually lead to development of AD. Adding to the decreased CBF and CBF velocity that routinely occurs in AD patients are physical changes in the external and internal characteristics of capillaries in the brains of these patients that cause hypoperfusion to cerebral neurons.

Histochemical studies have shown that capillaries in AD patients lose their structural configuration as these vessels become twisted and kinked, which markedly affects the microcirculatory flow pattern.\textsuperscript{23} Blood flow through an unaffected capillary is normally laminar, but if the capillary shape becomes irregular, as seen in capillary vessels in AD, the blood flow pattern through these vessels reverts from normal linear flow to abnormal disturbed flow. This irregular blood flow movement progressing through abnormally shaped capillaries becomes another factor that decreases CBF to critical neurons within the brain.

In addition to the abnormal laminar flow characteristics, there are changes that occur in the walls of capillaries that also adversely affect CBF. Physical abnormalities that occur within the vessel wall of capillaries of AD patients include basement membrane thickening, endothelial cell compression, pericyte degeneration, and vessel luminal distortion.\textsuperscript{16} These physical changes damage the endothelial cells lining the wall of the capillaries, resulting in a compromise of nitric oxide activity that normally occurs within these endothelial cells. Endothelial cells are extremely important in CBF flow because they control vascular dilation, which allows for an increase in CBF. When these endothelial cells lining the capillary walls are adversely affected, the lumen of the capillaries lose their ability to dilate and CBF becomes limited. This endothelial cell alteration, vascular smooth muscle cell atrophy, and distortion of small blood vessels in an AD brain, restrict CBF, resulting in cerebral hypoperfusion, which eventually may prove to be the critical issue in subsequent development of AD pathology.

**TREATMENT MODALITY**

Great amounts of time and money are currently being spent at many centers throughout the world to find a pharmaceutical method to address the neurologic and cognitive problems associated with AD. Multiple drug studies continue to be evaluated in the quest to find a therapeutic approach to AD. Cholinesterase inhibitors are currently in common use for this purpose, but it is well-known that their clinical effects are of short duration, even in patients who reportedly have responded to the drugs. Additionally, adverse side effects of cholinesterase inhibitors drugs can be considerable.\textsuperscript{24}

Despite the continuing belief by some investigators that amyloid plaque and, to a lesser degree, ACh deficiency are the underlying causes of AD, interest continues to increase in the belief that the underlying cause of AD might well prove to be hypoperfusion to the brain.\textsuperscript{25-28} Two factors generally accepted in AD etiology are advancing age and various risk factors that are known to decrease CBF. If decreased CBF can eventually prove to be the underlying basis for AD development, strenuous efforts should continue to be directed to devising methods, medical or surgical, to increase CBF and to learn its effect on patients. If decreased CBF is found to be the case, methods to increase blood flow to the brain must take the highest priority.

I am unaware of any pharmaceutical treatment that can increase CBF to a substantial degree for an extended period of time. There is now a surgical procedure that has been proved to be able to add a substantial amount of blood during a protracted period of time to the human brain.\textsuperscript{29} Of considerable importance is the fact that the operation has been shown to cause postoperative reversal of symptoms in AD patients.\textsuperscript{30-32} This operation, known as omental transposition (OT), is a procedure that deserves critical evaluation, especially for patients with late MCI and early AD patients.

OT is a surgical procedure in which the omentum is surgically lengthened into an extensive intact pedicle within the peritoneal cavity, with its blood supply remaining intact. The omental pedicle is then brought subcutaneously up the chest, neck, and behind the ear. A craniotomy is performed and the dura opened, followed by removing small portions of the pia mater. The omentum is then laid directly on the underlying brain and the craniotomy bone is replaced.\textsuperscript{33} Blood vessels have been shown histologically to penetrate directly, vertically, and rapidly from the omentum into the underlying brain within days after the procedure, allowing extracerebral blood and biologic substances derived from the omentum to enter the AD brain.\textsuperscript{34,35}

Important biologic agents are present in omental tissue, including neurotransmitters,\textsuperscript{36} nerve growth,\textsuperscript{37} and angi-
genic factors, especially vascular endothelial growth factor, which is the most angiogenic substance in the human body, with the greatest concentration of vascular endothelial growth factor being present in omental tissue. Of recent interest is the finding of large numbers of stem cells that are present in human omentum.

A pharmaceutical approach in the treatment of AD would certainly be more acceptable to patients, as opposed to a surgical procedure such as OT. If a patient today shows evidence of advanced MCI or early AD, the possibility of a favorable approach for relief of these conditions by any present-day treatment is quite limited. Unfortunately, no one knows how many years or decades it might take for a reliable pharmaceutical approach to AD to become a reality.

Although not a cure, OT has been shown to attain a favorable cognitive response for several years, with most patients in the late stages of AD. It seems reasonable to believe that if patients were operated earlier in the development of AD, an improved longterm postoperative result would be expected, because more viable neurons would be available for metabolic stabilization. Allowing a patient with AD to function with his family on a day-to-day basis during an extended time period would be a benefit of enormous proportion to family members, and would also be financially beneficial in the care and management of AD patients. Performing a small study involving OT on AD patients in a strictly controlled setting could be limited in number, because only six subjects are necessary for statistical analysis of results.

Based on patients who have undergone OT for AD, it would be expected that several patients in the study would have a favorable neurologic effect because of energizing of deteriorating cerebral neurons that are in the process of dying. OT has already been shown to be helpful in reversing symptoms in AD patients (9 of 25 patients have reversed symptoms, in my personal surgical experience), most of the patients being in the advanced stage of their disease. Unfortunately, none of these AD patients were involved in a randomized or controlled study.

One can expect that there would be AD patients who would choose to undergo OT under strict experimental control if they considered the possibility that the operation might have a favorable effect on their cognitive symptoms. Patients would be informed that the purpose of the operation is to increase blood flow and critical biologic substances into their AD brains, in the hope that the procedure would stabilize their condition and possibly reverse their cognitive symptoms.

Technical aspects of performing OT are not difficult when performed by a well-trained general and neurologic surgeon. As in all new surgical procedures, there are maneuvers that are important, and the team that performs OT should be aware of these maneuvers, so as not to lessen the chance of subsequent neurologic improvement. If the operation is performed by people without experience or awareness of the possible complexity of this operation, as in any operation, poor postoperative results can result. If this occurs, it can lead to the reporting that the operation is difficult, unsafe, and without clinical justification—comments that are unjustified.

In conclusion, AD develops from decreased CBF, and OT has the potential to be helpful to an AD patient by adding a substantial amount of CBF and critical biologic agents to their AD brain. Because of the devastating nature of AD to both patient and family, it would appear that a well-controlled study involving a small number of AD patients is not only justified, but appears necessary. A favorable result from such a study could prove very important.

Khachaturian recently described the remarkable advances that have been made in the last 20 years in knowledge pertaining to AD. Unfortunately, no comparable advances have been made in the therapeutic area. OT appears worthy of evaluation until pharmacological methods are developed to prevent and treat AD.

REFERENCES


