

Editorial

Alzheimer's Disease: A Decreased Cerebral Blood Flow to Critical Intraneuronal Elements Is the Cause

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Abstract. Normally, an adequate cerebral blood flow arrives at individual cerebral neurons in which the blood flow augments activity of intraneuronal mitochondria, which is the source of intraneuronal ATP, the energy source of cerebral neurons. With a decrease in cerebral blood flow that can occur as a function of normal aging phenomena, less blood results in decreased mitochondria, decreased ATP, and a decrease in neuronal activity, which can eventually lead to Alzheimer's disease. It has been found that placement of the omentum directly on an Alzheimer's disease brain can lead to improved cognitive function.

Keywords: ATP, cerebral blood flow, mitochondria, omentum

Of the many major problems presently confronting the worldwide medical community, one is how to control and treat Alzheimer's disease (AD). In the United States, AD is diagnosed at the rate of 400,000–500,000 cases per year. During the past several decades widespread interest has led to attempts to implicate amyloid deposits in the brain as the cause of AD. These attempts have been unsuccessful due mainly to two observations made at autopsy: 1) the percentage of amyloid plaques within the brains of non-demented age-adjusted individuals had the same percentage of amyloid plaques found within the brains of AD patients [1], and 2) no relationship was found between the number of amyloid plaques located in the brains of AD patients and their degree of dementia severity [2], although this could change over time. Observations have weakened the theory

that amyloid is the basis for AD, but the theory persists as was recently noted in a paper (May 6, 2021) in the *New England Journal of Medicine* stating “if anti-amyloid treatment is shown to be successful, precise staging of AD may be required.” [3]

More recently, the U.S. Food and Drug Administration (FDA) approved a new drug (Aduhelm) produced by the Biogen Company that claims the drug has the potential to remove amyloid from the brain. However, members of the entire biostatistical department of the FDA said there was insufficient evidence to support approval of the drug. Significantly, three members of the FDA's Advisory Committee resigned immediately after the FDA approved the drug. Thousands of papers published over several decades have attempted to implicate amyloid as the cause of AD, yet all anti-amyloid treatments have failed. This paper will propose that amyloid is not the cause of AD and that decreased cerebral blood flow (CBF) is the basis for AD.

The vascular theory that AD is treatable is based on the brain's continuing need for CBF especially in

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the presence of advancing age. The theory originated in the late 1970s when it was shown that placement of the omentum on the brains of dogs [4] and monkeys [5] prevented strokes in these animals even in the presence of the ligation of their middle cerebral artery. Additionally, a small group of stroke patients showed cognitive improvement after application of the omentum to their brain [6]. It seemed obvious that these neurological changes in animals and humans were due to the placement of the omentum on their brains.

The omentum was chosen because it is the most angiogenic tissue in the body [7] and there was no other method, then or now, that can markedly increase CBF. Blood flow studies were undertaken and placement of the omentum on the brain of humans showed that increased CBF originating from the omentum resulted in a major increase in CBF throughout the brain over an increased and indefinite period of time [8].

During that time of research and publications, this author received a copy of an unsolicited letter from Dr. William Regelson, Professor of Medicine at the Medical College of Virginia. The letter was three pages in length and was addressed to the Alzheimer's Association. The length of the letter precludes its full content, but the first sentence of the letter stated, "I am sorry for having felt the need to importune on your time, but the clinical observations made by Harry Goldsmith, M.D. require the particular and the immediate attention of your organization." The last sentence of Dr. Regelson's letter stated, "in the meantime I hope that you and your colleagues in review of the data and examination of patients, will recognize (sic) that the OT (Omental Transposition) has succeeded in providing significant clinical improvement." This letter was sent directly to the attention of the Alzheimer's Association on December 1, 1999, with expectation that it would stimulate the association's interest in omental transposition to the AD brain. However, nothing transpired.

In the hope that interest would provoke a desire to learn how the omentum functioned on the brain of AD patients, several omentum papers were published [9–16]. In a final attempt to stimulate investigative interest in the omentum as a treatment of AD, a major paper was published, titled, "Alzheimer's Disease Can Be Treated-Why the Delay?" [17] The paper generated great interest with the Internet reporting more than 11,000 views by readers. Given this large number, it would appear that anyone with interest in the treatment of AD would have been aware of the information in the publication. This paper was

published in 2017, and now, four years later, there continues to be no interest by the Alzheimer's Association in the omental treatment for AD. Why has there been such lack of interest especially since it has now been reported that placement of the omentum on the brain of cerebrovascular patients has led to functional recovery after cerebrovascular disease [18]?

If interest and investigative evidence had been shown 22 years ago following Dr. Regelson's letter to the Alzheimer's Association, information could have been ascertained as to whether the omentum demonstrated clinical improvement, or failure, for cognitively impaired AD patients. During this 22-year period, approximately 8 million people in the United States were diagnosed with AD. If they had been made aware that placement of the omentum on the AD brain had been found to be cognitively effective, some of these people might have experienced improvement in their cognitive ability.

In a personal study of 25 patients who underwent omental transposition to their AD brain, nine had significant cognitive improvement, ten showed minimal improvement, and six patients showed no improvement following the operation. The patients who showed no or only minimal improvement were carefully studied post-operatively to learn the possible reason for the negative result of the surgery and the following was learned: patients should not be operated upon if they are older than 80, have had AD for over several years, and, most importantly, their Mini-Mental State Examination score should never be below 14–15. The Mini-Mental State Examination score is important because a high numbered score indicates a greater number of viable deteriorating neurons in the AD brain whereas, a low score indicates a greater number of dead neurons in an AD brain which makes it highly unlikely that an operation would be successful.

The goal of researchers working in the field of AD is to understand the origin of AD and, even more importantly, to develop a treatment to improve the cognitive capabilities of AD patients. It is possible that these two goals can be met.

DEVELOPMENT OF ALZHEIMER'S DISEASE

The main problem in AD is the known decrease in CBF. Spin-labeled resonance MRI [19] and other blood flow studies [20, 21] confirmed a marked

decrease in CBF in patients with AD when compared to age-matched controls. MRI studies measuring the total volume of CBF that flowed to the brain of AD patients through the internal carotid and basilar arteries revealed a significant decrease in the volume of blood flow through these arteries. AD patients exhibited a mean blood flow of 442 mL/min as compared to a mean blood flow of 551 mL/min in nondemented, age-matched participants ($p > 0.001$). Comparable studies in a younger age group of normal participants (median age 29 years) by phase contrast MRI studies demonstrated an even higher mean blood flow of 742 mL/min.

A significant decrease in CBF is a reflection of the normal aging process. Various factors causing this situation are a decreased cardiac ejection fraction, a decrease in cerebral capillary density [22], and changes in small blood vessels in the AD brain that have become twisted, kinked, and looped [23]. The CBF that flows into the brain perfuses intraneuronal mitochondria, which controls intraneuronal adenosine triphosphate (ATP) production, ATP being the critical energy source of each cerebral neuron. The relationship between mitochondria and ATP is critical since cellular energy within cerebral neurons is vital and must be maintained. When there is a significant decrease in ATP, caused by a lessening support of mitochondria, a lowering in energy activity occurs in each neuron. This results in a decrease in biological substances into the neuron, such as oxygen and glucose, that are necessary for neuronal survival. It is the marked decrease in CBF that adversely affects intraneuronal mitochondria that is the producer of ATP, the source of cellular activity.

When normal physiological activity occurs within the brain, adequate cerebral blood flows to intraneuronal mitochondria that supports the production of ATP [24], the source of cellular energy. A complete physiological reversal results in AD. When inadequate CBF is presented to a cerebral neuron, ATP decreases, cellular inactivity occurs, and the potential for AD can develop.

TREATMENT OF ALZHEIMER'S DISEASE

The relationship between decreased CBF, mitochondria, and ATP appears to be the basis for AD. The key to this relationship is the attempt to treat AD by increasing CBF in an amount of blood flow that is significant in volume and persistent over time. Placement of the omentum on the surface of an AD

brain results in a large volume of blood that enters the brain. This increased CBF would favorably affect the intraneuronal mitochondria, which would benefit production of ATP. This vascular concept for the treatment of AD is not a theory. It has been shown to be effective in post-operative AD patients who personally reported the success of the operation in written testimonials [25]. A decrease in CBF apparently can cause AD, but an increase in CBF can achieve cognitive improvement in AD patients.

CONCLUSION

AD develops as a result of age-related consequences. It has been shown by spin-labeled MRIs that there is a significant decrease in CBF in AD patients when compared to normal age-related populations. AD develops when cerebral neurons lose the cellular energy that is necessary for their survival. Cellular energy activity is provided by intraneuronal ATP which is controlled by intraneuronal mitochondria. Any factors that lessen CBF can result in a direct loss of the ability of mitochondria to produce ATP, the energy source of the neuron. Factors that limit CBF can diminish cellular energy for an indefinite period, causing the development of AD. These factors can include a depressed cardiac ejection fraction, a decrease in capillary density in AD [22], and conditions in small cerebral blood vessels that can result in the loss of a smooth flow of blood to critical neurons in the AD brain [23]. If a treatment for AD is to be accomplished, a major increase in CBF must be developed. This can be achieved when the omentum, with its large blood supply, is applied directly onto an AD brain. Laparoscopic harvesting of the omentum to be placed on the brain can make the surgical operation easier to perform [26]. It would appear that a major research effort must now be instituted to confirm or negate that AD is the result of a decrease in CBF. There should no longer be a delay in carrying out this investigative effort.

DISCLOSURE STATEMENT

The author's disclosure is available online (<https://www.j-alz.com/manuscript-disclosures/21-5479r1>).

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