

Editorial

Alzheimer’s disease can be treated: Why the delay?

Harry S. Goldsmith

Department of Neurological Surgery, University of California, Davis, Sacramento, California, USA

E-mail: *Harry S. Goldsmith - hlgldsmith@aol.com

*Corresponding author

Received: 24 March 17 Accepted: 04 May 17 Published: 07 July 17

Key Words: Alzheimer's disease, cerebral blood flow, deteriorating neurons, omentum

INTRODUCTION

Thousands of published papers have continued to report that amyloid deposition in the brain of Alzheimer disease (AD) patients is the basis for the disease. Two observations deserve attention. It has been found at autopsy that the percentage of amyloid plaques within the brains of nondemented, age-adjusted individuals can be the same percentage of amyloid plaques found at autopsy within the brains of AD patients.^[3] Another study found no relationship between the number of amyloid plaques located in the brains of AD patients and their degree of dementia severity.^[36] These findings clearly challenge the presumption that the presence of amyloid in the AD brain is the basis for the disease.

There is an increasing consideration that a decrease in cerebral blood flow (CBF) may be the cause of dementia in AD. The decrease in CBF typically found in AD has long been believed to be due to the death of critical neurons which, because of their nonviability, no longer required a sustainable CBF. An alternative explanation to this idea is that it is not dead or dying neurons that cause the decrease in CBF, but it is the actual decrease in CBF over a prolonged period that results in the death of critical neurons in AD.


Spin-labeled magnetic resonance studies have confirmed the marked decline in CBF in AD as compared to age-matched controls.^[1] Further magnetic resonance imaging (MRI) studies measured the total volume of CBF that flowed to the brain of AD patients through the internal carotid and basilar arteries. A significant decrease in the volume of blood flow through these arteries was noted in AD patients who 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.^[33,34]

Among the multiple causes of the decreasing CBF found in AD is the weakened cardiac function which normally occurs with aging. In addition to a decreased cardiac ejection fraction is a decrease in cerebral capillary density in AD.^[2] There are also associated physical changes in small blood vessels in the AD brain that have become twisted, kinked, and looped.^[9] These conditions in small cerebral blood vessels restrain a sustainable and smooth flow of blood to critical neurons in the AD brain.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Access this article online	
Quick Response Code: 	Website: www.surgicalneurologyint.com
	DOI: 10.4103/sni.sni_116_17

How to cite this article: Goldsmith HS. Alzheimer's disease can be treated: Why the delay? Surg Neurol Int 2017;8:133.
<http://surgicalneurologyint.com/Alzheimer's-disease-can-be-treated:-Why-the-delay?/>

How decreased blood flow causes the dementia in AD depends on the individual energy requirements of critical cerebral neurons. Neurons maintain their survival through intraneuronal energy activity that is under the control of intraneuronal mitochondria.^[6] Any marked decrease in CBF adversely affects intraneuronal mitochondria, which limits production of adenosine triphosphate (ATP) production, ATP being the energy source of neurons. As ATP production decreases due to mitochondrial limitation, any associated decrease in CBF will affect oxygenation, lower glucose levels, and limit biological substances that normally are delivered to the brain. An adequate CBF is crucial to maintaining the energy requirements of individual cerebral neurons.

Based on the possibility that decreased CBF could be the cause of AD, a method was developed to introduce a large volume of blood directly into the AD brain to compensate for the decreased CBF which routinely occurs in AD. As there is presently no pharmaceutical agent that can increase CBF over an extended period, it was believed that an increase in CBF could be accomplished by a surgical procedure.

The surgical procedure that was developed involves placement of a piece of the patient's intact omentum directly on the brain. The operation was named omentum transposition (OT) to the AD brain. Clinical studies had previously shown that the operation was safe and could introduce a large volume of CBF into the brain over an extended period.^[14] One of the reasons that the omentum was chosen to increase CBF was the large amount of vascular endothelial growth factor (VEGF) known to be present in omental tissue. VEGF is the most angiogenic substance in the body and its volume in the omentum is eight times greater than in any other area of the body.^[38]

Early studies had shown that placing the omentum on the brains of dogs^[11] and monkeys^[12] resulted in an increase of blood flow into the brain. This increased CBF from the omentum prevented cerebral infarcts (strokes) in these animals despite the ligation of their middle cerebral artery. In addition to the animal experiments, a small group of late-stage stroke patients underwent successful OT to the brain as evidenced by improvement in their functional and speech conditions.^[13,17] These clinical observations in both animals and humans appeared to justify placing the omentum on the brain of Alzheimer patients.

Twenty-five AD patients underwent OT to the brain. Six patients demonstrated no neurological improvement; 10 patients demonstrated minor neurological changes, and nine patients experienced significant improvement in their cognitive status. The patients who showed little or no improvement after OT were those who had AD for more than 5 years.^[27] In addition, the mini-mental state exam (MMSE) scores of these patients were not taken

into account at the time of their preoperative evaluation. As a result of this serious oversight, some of the patients underwent the surgery with an MMSE score as low as 2. It has since been determined that AD patients with an MMSE score below 14–15 have a low expectation for postoperative cognitive improvement.

As efforts continue to focus on the theory that amyloid is the cause for AD, a therapeutic approach involving amyloid has yet to be established to treat AD. Unfortunately, there has been little interest in exploring the possibility that a surgical procedure (OT) could increase CBF to the AD brain and improve cognitive function. Because many believe that amyloid is the basis for AD, research efforts using a variety of drugs have been administered in the attempt to remove amyloid plaque from the brains of AD patients, but drugs have proven unsuccessful and occasionally proved dangerous.^[10] OT appears to be a reasonable approach in attempting to discover a possible treatment for AD.

Our laboratory demonstrated the enormous absorbability of the omentum by placing an intact omental pedicle from an animal into a beaker of saline in which India ink had been added. The India ink was observed in omental lymphatics within thirty seconds.^[23] A much earlier paper was published almost a century ago (1931) by Batchelder, Field, and Drinker from Harvard titled, "Absorption of Particulate Matter by Omentum."^[4] They reported that when an intact omental pedicle from an animal was placed in a beaker filled with saline into which small iron particles had been added, the iron particles were found in the liver within one hour. It seems reasonable to believe that if the liver had been examined in less than 1 h, it is likely that iron particles would have been discovered in the liver at that time. Given the enormous absorbability of the omentum, studies have shown that the rapid absorption of India ink and iron particles, by the omentum, might have the potential to absorb amyloid in the AD brain.

It has recently been shown in humans that amyloid can be removed from the brain by various clearing systems, most likely by transport across the blood brain barrier and meningeal lymphatic vessels.^[35] However, since large amounts of amyloid can accumulate in the AD brain, clearing processes appear to be very slow. Absorption of amyloid from the AD brain by drugs has been the long-term goal of pharmaceutical corporations, but as previously shown, the drugs that have been attempted for this goal have failed.^[10] The known ability of the omentum to increase CBF and possibly absorb amyloid may prove to be major factors in the future treatment of AD.

CONCLUSION

OT to the AD brain is a procedure that has been shown to offer a patient with AD the possibility of improved

cognitive function. A new book (see addendum below); however, has claimed that there is no treatment for AD. This statement is not supported by scientific data and, hopefully, will not cause researchers to discontinue their efforts to find new and successful ways to treat AD patients.

Addendum

A recent book has been written by Dr. de la Torre (DLT). On page one in this book is the statement “There is no cure for AD and no hope for recovery.” The book, *Alzheimer’s Turning Point: A Vascular Approach to Clinical Prevention*,^[8] is well written; however, it may have a seriously negative impact on future efforts by clinical investigators in their quest to develop new ideas and methods to treat AD. It would be difficult to continue one’s effort in this AD area of medicine when the treatment for the disease had been reported to be untreatable and incurable.

DLT firmly believes that AD is untreatable and therefore future efforts should be focused only on the prevention of the disease. He states in his book (on page 6) and in other publications that once AD is diagnosed, there is no treatment to improve the condition. In 2010, DLT clearly stated his belief in his paper titled, “Alzheimer’s Disease Is Incurable but Preventable.”^[7] An opposing viewpoint was subsequently published in an effort to decrease the negative effect of DLT’s paper. This paper was published in 2014 under the title “Benefit of Omental Blood Flow in Alzheimer’s Disease: Effect on Deteriorating Neurons.”^[26] This latter paper was not referenced in DLT’s book nor was the omentum even mentioned in his book.

DLT has stated that “AD is irreversible because the neurons that locally control function are likely dead, and dead neurons cannot be brought back to life.”^[7] Obviously, there is no treatment to restore life to dead neurons. If an increase in cognition in the AD brain is to be produced, it would require an increase in CBF and other nutrient substances to be presented to deteriorating viable neurons that remain in the AD brain.

There are three types of neurons in an AD brain: normal functioning neurons, deteriorating neurons, and dead neurons. In the early stage of AD there is a greater number of viable deteriorating neurons and in the later stages of AD a greater number of dead neurons. DLT apparently believes that all neurons are dead, even in the earlier stages of AD. However, deteriorating neurons in the AD brain are present in number depending on the stage of the disease. Early in AD at the lamina-level 2 in the entorinal cortex, 60% of the neurons are of the deteriorating type, and at lamina-level 4, 40% are of the deteriorating type.^[25] The number of deteriorating neurons remaining in the entorinal cortex is important because critical cognition produced in this area is commonly damaged in the early stages of AD. Providing

increased CBF by omental transposition to deteriorating neurons involved in the entorinal cortex may explain why omental placement on the AD brain has resulted in improved cognitive function reported in multiple AD patients.^[13-27,31,32,39]

Cognitive improvement following omental transposition to the AD brain has been reported in various journals including *The Journal of Alzheimer’s Disease* (JAD). Two articles published in JAD reported the successful result of OT to the AD brain.^[22,29] DLT had to be aware of these articles since he is a senior editor of JAD.

In DLT’s book (page 6), he recounts the history of a patient with early AD and the frustration and difficulties of the patient’s wife in caring for her husband. What was not reported in the book was when the patient was in the advanced stage of AD, having institutionalized for months and no longer recognizing his wife, he subsequently underwent omental transposition to his AD brain and had excellent postoperative cognitive results. The significant cognitive improvement by the patient stimulated his wife to write a book, titled *Alzheimer’s Surgery: An Intimate Portrait*,^[37] which described the success of the surgical procedure. The patient’s cognitive postoperative result was so impressive that he appeared on national television. The patient’s postoperative changes from his previous AD condition, which had been confirmed by a brain biopsy, demonstrated that AD is a disease that is treatable. These changes were not mentioned in DLT’s book.

In 1964^[30] and in 1976,^[29] several Scandinavian researchers demonstrated that decreased CBF in humans led to decreased cognitive function. In 1993, doctors DLT and Mussivand confirmed these observations in their seminal paper which showed that old rats with decreased CBF, caused by carotid ligation, demonstrated decreased cognitive function when placed in a water maze.^[5]

The comments that have been made in this addendum are not meant to diminish the many contributions that DLT has made in our understanding of the physiological mechanisms involved in AD. The comments listed in this addendum have been made solely, thoughtfully, and hopefully to discourage research and clinical investigators from abandoning their efforts to develop ideas and future treatments for AD patients in view of comments that AD is untreatable and incurable. We must continue to search for future treatments for patients with AD. The greatest gift one can give a patient with AD is the possibility that their cognitive condition can be improved. This is the hope for anyone with AD.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Alsop DC, Derre JA, Grossman MM. Assessment of cerebral blood flow in Alzheimer's disease by disease by spin-labeled magnetic resonance imaging. *Ann Neurol* 2000;47:93-100.
2. Ambrose CT. A therapeutic approach for senile dementias; neuroangiogenesis. *J Alzheimer Dis* 2015;43:1-17.
3. Arriagado PV, Growdon JH, Hedley-White ET, Hyman B. Neurofibrillary tangles but not senile plaques parallel: Duration and severity of Alzheimer disease. *Neurology* 1992;42:631-9.
4. Batchelder AD, Field ME, Drinker CK. Absorption of particulate matter by omentum. *J Exp Med* 1931;53:641-5.
5. de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease. *Neurol Res* 1993;15:146-53.
6. de la Torre JC. Cerebral hypoperfusion capillary degeneration development of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2000;14:573-81.
7. de la Torre JC. Alzheimer disease is incurable but preventable. *J Alzheimer Dis* 2010;20:861-70.
8. de la Torre JC. In: *Alzheimer's Turning Point: A Vascular Approach to Clinical Prevention*. Switzerland: Springer Publishing; 2016. p. 160
9. Fisher VW, Siddigia A, Yusufaly Y. Altered abnormalities in selected areas of brain with Alzheimer disease. *Acta Neuropathol* 1990;79:672-9.
10. Gilman S, Koller M, Black RS, Jenkins L. Clinical effects of a beta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* 2005;64:1553-62.
11. Goldsmith HS, Duckett S, Chen WF. Prevention of cerebral infarction in the dog by intact omentum. *Am J Surg* 1975;130:317-26.
12. Goldsmith HS, Duckett S, Chen WF. Prevention of cerebral infarction in the monkey by omental transposition to the brain. *Stroke* 1978;147:503-6.
13. Goldsmith HS, Saunders RL, Reeves AG, Allen CD, Milne J. Omental transposition to brain of stroke patients. *Stroke* 1979;10:471-2.
14. Goldsmith HS, Bacchi P, Cossu M, Pau A, Rodriguez G, Rosadini G, et al. Regional cerebral blood flow after omental transposition to the ischemic brain in man: A five-year follow-up study. *Acta Neurochir* 1990;106:145-52.
15. Goldsmith HS. Omental transposition for Alzheimer's disease. *Neurol Res* 1996;18:103-8.
16. Goldsmith HS. Omental transposition to the brain for Alzheimer's disease. In: *Cerebrovascular Pathology in Alzheimer's Disease*. *Ann N Y Acad Sci* 1997;826:323-36.
17. Goldsmith HS, Sax DS. Omental transposition for cerebral infarction: A thirteen-year follow-up study. *Surg Neurol* 1999;51:342-5.
18. Goldsmith HS. Omental transposition to the brain for Alzheimer's disease. In: Goldsmith HS, editor. *The Omentum: Application to Brain and Spinal Cord*. Forefront Publishing: Wilton, CT; 200. p. 184-97.
19. Goldsmith HS. Role of the omentum in the treatment of Alzheimer's disease. *Neurol Res* 2001;23:555-64.
20. Goldsmith HS. Treatment of Alzheimer's disease by transposition of the omentum. In: *Alzheimer's Disease: Vascular Etiology and Pathology*. *Ann N Y Acad Sci* 2002;977:454-67.
21. Goldsmith HS, Wu W, Zhong J, Edgar M. Omental transposition to the brain as a surgical method for treating Alzheimer's disease. *Neurol Res* 2003;25:625-34.
22. Goldsmith HS. Omental transposition in treatment of Alzheimer disease. *J Am Coll Surg* 2007;205:800-4.
23. Goldsmith HS. Application of the omentum to the brain and spinal cord (chapter 3). In: Goldsmith HS, Ed., *The Omentum: Basic Research and Clinical Applications*. Woodbury, CT: Cine-Med Publishing; 2010. p. 37-52.
24. Goldsmith HS. Omental transposition to the brain for Alzheimer disease. In: Goldsmith HS, editor. *The Omentum: Basic Research and Clinical Applications*. Woodbury, CT: Cine-Med Publishing; 2010. p. 231-5.
25. Goldsmith HS. A new approach to the treatment of Alzheimer's disease: The need for a controlled study. *J Alzheimer Dis* 2011;25:209-12.
26. Goldsmith HS. Benefit of omental flow in Alzheimer disease: Effect of deteriorating neurons. *J Alzheimer Dis* 2014;42:S277-80.
27. Goldsmith HS. Omentum transposition for treatment of Alzheimer's disease in China. *Chinese Neurosurg J* 2016;2:1-3.
28. Gomez-Isla TI, Price JL, McKeel DW, Morris JC, Growdon JH, Hyman BT. Profound loss of layer 2 entorhinal cortex occurs in very mild Alzheimer disease. *J Neurosci* 1996;16:4491-500.
29. Gustafson L, Hagberg B. Emotional behavior, personality changes and cognitive reduction in presenile dementia: Related to regional cerebral blood flow. *Acta Psychiatr Scand* 1975;51:36-71.
30. Hedlund S, Kohler V, Nylin T, Olsson R, Regnstrom O, Rothstrom E, et al. Cerebral blood circulation in dementia. *Acta Psychiatr Scand* 1964;40:77-106.
31. Shankle WR, Hara J, Bjornsen I, Gade JF, Lepore PC, Ali MB, et al. Omentum transposition surgery for patients with Alzheimer's disease: A case series. *Neuro Res* 2008;30:313-5.
32. Shankle WR, Hara J, Bjornsen I, Gade JF, Lepore PC, Ali MB, et al. Omentum therapy for primary progressive aphasia with tau negative histopathology: 3 year study. *Neurol Res* 2009;31:766-9.
33. Spilt A, Bok FMA, Van der Geest RJ, Reiber JH, Kunz P, Kamper AM, et al. Reproducibility of total cerebral blood flow measurements using phase contrast magnetic resonance imaging. *J Magn Reson Imaging* 2002;16:1-5.
34. Spilt A, Weverling-Rijnburger AWE, Middelkoop HAM, van Der Flier WM, Gussekloo J, de Craen AJ, et al. Late-onset dementia: Structural brain damage and total cerebral blood flow. *Radiology* 2005;236:990-5.
35. Tarasoff-Conway JM, Carrare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, et al. Clearance systems in the brain: Implications for Alzheimer disease. *Nat Rev Neurol* 2015;11:457-470.
36. Terry RD, Masliah E, Salmon DP. Physical basis of cognitive alterations in Alzheimer disease: Synapse loss is the major correlate of cognitive impairment. *Ann Neurol* 1991;30:572-80.
37. Weiss B. In: *Alzheimer Surgery: An Intimate Portrait*. Bloomington, IN: Authorhouse Publishers; 2006.
38. Zhang QX, Magovern CJ, Mack CA, Budenbender KT, Ko W, Rosengart TK. Vascular endothelial growth factor is the major angiogenic factor in omentum mechanism of the omentum-mediated angiogenesis. *J Surg Res* 1997;67:147-54.
39. Zhong J, Wu WI, Goldsmith HS. Preliminary study of omentum transposition to brain for treatment of Alzheimer's disease. *J Shanghai Med Univ* 2007;19:46-51.