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Maintaining Mental Acuity: How Our Lifestyle Decisions Can Prevent Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is a highly prevalent neurodegenerative condition in the elderly population and is the leading cause of dementia. Despite available symptomatic treatments, the cure remains elusive. Recent research has established a strong correlation between vascular atherosclerosis and Alzheimer's disease, generating hypotheses that describe it as a disorder of vascular origin. This approach highlights the possibility of intervening in the prevention and slowing down of its progression through the control of vascular risk factors, and that the control of these same factors could have a positive impact in the natural history of the disease.

In addition, genetic factors such as the ApoE4 gene, influence the risk, which is why diet and lifestyle modifications can also modulate this risk. Faced with the dim prospect of an imminent cure, prevention emerges as a fundamental strategy to provide a better quality of life for those affected by Alzheimer's disease.

DEFINITION

Alzheimer's disease (AD) is a neurodegenerative disorder of uncertain cause and pathogenesis that mainly affects older adults and the most common cause of dementia (1). The most representative, and often the earliest presentation, is the selective memory impairment, although there are certain exceptions. Treatments are now available that can improve some symptoms and slow the progression of the disease, but there is no cure, so the disease inevitably progresses in all patients.

THE HISTORIC CASE OF AUGUSTE DETER

In 1901, Auguste Deter was taken to an insane asylum in Frankfurt, Germany, by her husband. She was described as a delirious, forgetful, and disoriented woman who was unable to perform her household chores. Attended by Dr. Alzheimer,

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she would become the case that would make him a household name around the world. In the autopsy made on Auguste, Dr. Alzheimer described histopathologic characteristics known for us today and characteristic of the disease, but it is overlooked that he also described atherosclerotic changes within the arteries of Auguste's brain (2).

POSSIBLE VASCULAR NATURE OF ALZHEIMER'S DISEASE

We commonly associate atherosclerosis with heart diseases, but this disease affects virtually the entire vascular system of the human body. An example of this systemic nature is the connection between coronary artery disease, brain degeneration and dementia (3).

Today we have a solid body of evidence that establishes a strong association between atherosclerotic vascular disease and the leading cause of dementia, Alzheimer's disease. For example, in the study by Roher A., et al, where arteries of the circle of Willis were analyzed in post-mortem patients, atherosclerotic blockage of the arteries was more extensive in Alzheimer's disease (AD) group than in the control group without dementia (4) (Figure 1).

In this same study, it is mentioned that mechanical obstructions and reduced blood flow in cerebral arteries due to atherosclerotic lesions damage the microvasculature, eventually leading to severe cerebral hypoxia, leukoaraiosis, lacunar infarcts, cerebral atrophy, ventricular dilatation, cerebrospinal fluid retention and noxious substances. The cumulative effects of these interdependent hemodynamic and hydrodynamic dysfunctions play a crucial role in accelerating and enhancing the pathogenesis and progression of Alzheimer's disease.

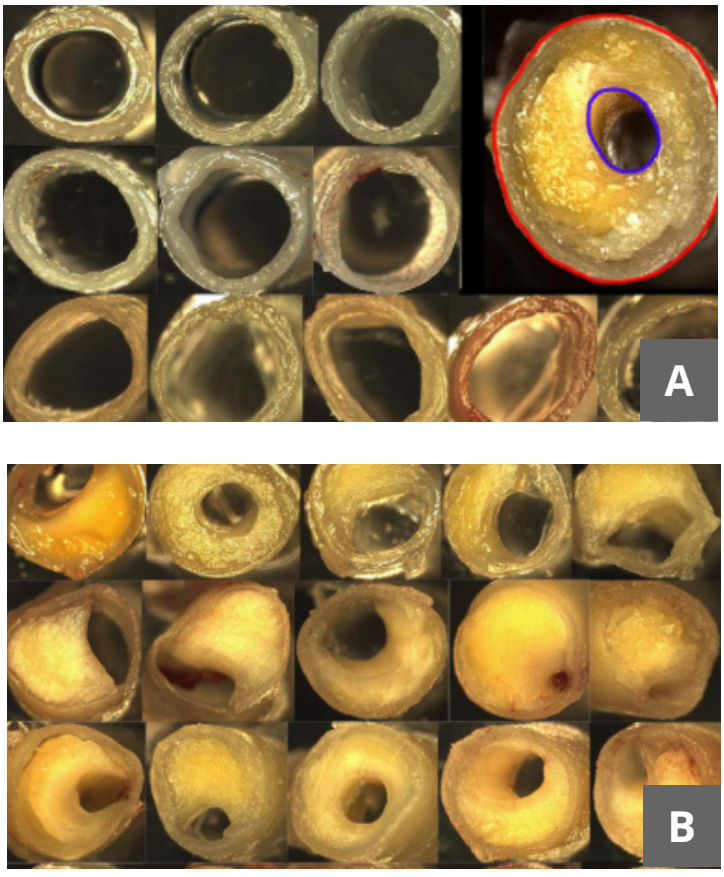

Figure 1. Representative axial sections of the arteries of the circle of Willis. The upper panel (A) illustrates a series of arterial sections in which the luminal area is minimally reduced. The lower panel (B) shows arteries with severe atherosclerosis. In some instances, arteries are almost completely obstructed by atheromatous plaque. Taken from Roher, A. E. (2011). Intracranial atherosclerosis as a contributing factor to Alzheimer 's disease dementia. Alzheimer 's & Dementia: The Journal of the Alzheimer's Association, 7(4), 436–444.

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Cerebrovascular atherosclerosis is notoriously more common and severe in people with Alzheimer's disease in comparison to those who are in the process of normal aging or who have other neurodegenerative diseases (5).

These types of findings are observed in several studies, so often that some authors have even considered for this disease to be reclassified as a vascular disorder (6).

This approach is positive, not because Alzheimer's disease is misclassified, but because, by comprehending it as a condition of vascular origin, we could take measures to prevent it or slow its progression as much as possible, since atherosclerosis is a potentially reversible disease.

And, as mentioned in the article, the intersection between vascular cognitive affection impairment and Alzheimer disease suggests that strategies that have been shown to be effective in delaying the progression of vascular disorders may prove beneficial in preventing or treating Alzheimer's disease.

How can this relate with cognitive function?

In the prospective study published by Zhu J. et al, to determine the impact of intracranial artery narrowing on progression from mild cognitive impairment to Alzheimer disease (AD), Zhu and researchers followed cognitively deteriorated individuals for four years, using computed tomography angiography (CT-angiography) methods to perform follow-up assessments of narrowing in major intracranial arteries to evaluate whether intracranial artery narrowing increased the risk of progression from mild cognitive impairment to Alzheimer's dementia.

They found that the cognition of those with less atherosclerosis in their brains remained stable over the years, whereas participants with higher cholesterol accumulation worsened, and those with the most severe obstruction declined rapidly **(Figure 2A)**. And the same was true for the ability to perform activities of daily living **(Figure 2B)**. Moreover, it doubled the progression of Alzheimer disease **(Figure 3),**

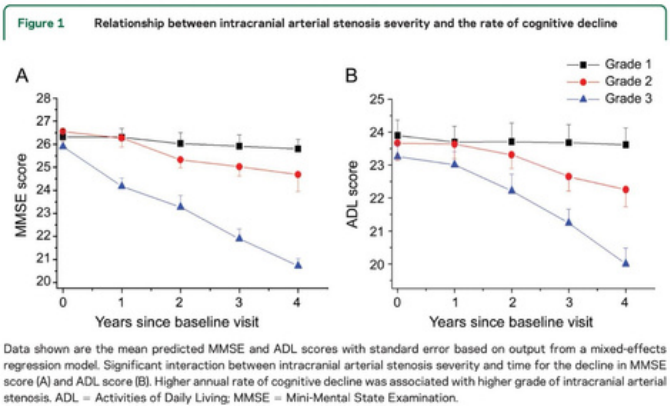

Figure 2. Relationship between severity of intracranial arterial stenosis and rate of cognitive impairment. Data shown are mean predicted MMSE and ADL scores with standard error based on the output of a mixed-effects regression model. A significant interaction between severity of intracranial arterial stenosis and time was observed in the decline of MMSE score (A) and ADL score (B). A higher annual rate of cognitive decline was associated with a higher grade of intracranial arterial stenosis. ADL = Activities of Daily Living; MMSE = Mini-Mental State Examination. Taken from Zhu, J. (2014). Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease. Neurology, 82(10), 842–849.

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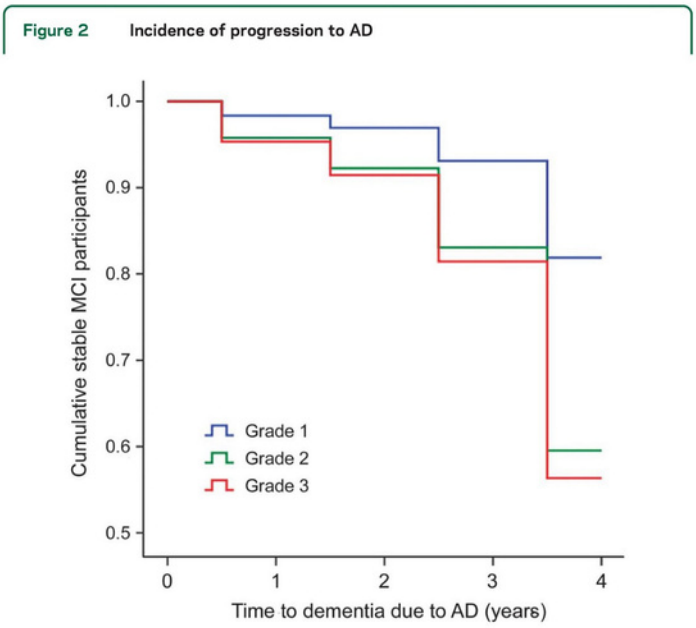

Kaplan-Meier curves for AD progression among subjects with MCI grouped according to intracranial arterial stenosis severity. Green and red lines indicate participants with grades 2 and 3 intracranial arterial stenosis, respectively. The blue line indicates participants with grade 1 intracranial arterial stenosis. The *p* value is 0.028 comparing participants with grade 2 to those with grade 1 intracranial arterial stenosis and 0.043 comparing participants with grade 3 to those with grade 1 intracranial arterial stenosis. AD = Alzheimer disease; MCI = mild cognitive impairment.

Figure 3. Incidence of Alzheimer's disease (AD) progression. Kaplan-Meier curves for Alzheimer's disease (AD) progression among subjects with mild cognitive impairment (MCI) grouped according to severity of intracranial arterial stenosis. Green and red lines indicate participants with grades 2 and 3 intracranial, respectively. The blue line indicates participants with grade 1 intracranial arterial stenosis. The p value is 0.028 when comparing with grade 2 with those with grade 1 intracranial arterial stenosis and 0.043 comparing participants with grade 3 to those with grade 1 intracranial arterial stenosis. AD = Alzheimer disease; MCI = mild cognitive impairment. Taken from Zhu, J. (2014). Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease. Neurology, 82(10), 842–849.

The interrogation is: Can this approach aimed at mitigating vascular risk factors make a significant difference?

Deschaintre, Y. et al. conducted a study with 301 patients divided into four groups; those without associated risk factors; patients without treatment; patients with few risk factors treated; and patients with all risk factors under treatment. These risk factors included hypertension (blood pressure >140/>90), dyslipidemia, DM (type I or II), smoking and atherosclerotic disease (8).

What the study revealed **(Figure 4)** was that patients who received treatment for their cardiovascular risk factors experienced a significantly lower decline and a slower course of the disease in comparison to those who received no treatment at all.

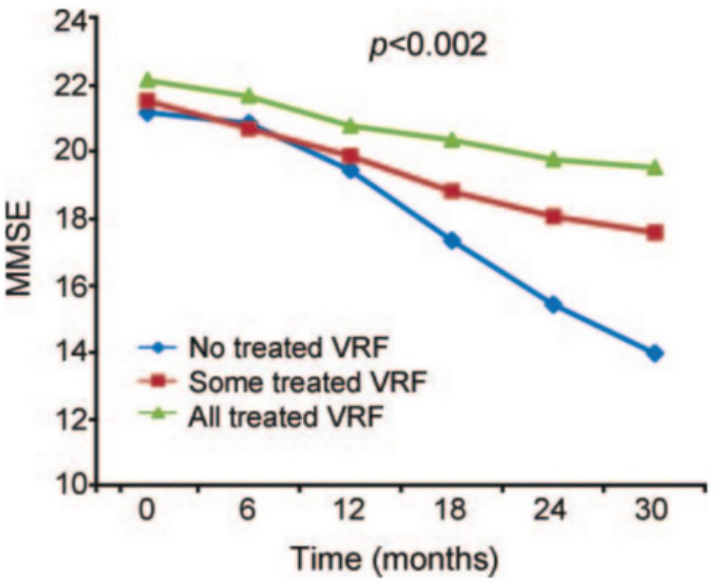

Figure 4. Multivariate mixed-effects regression model for MMSE progression over time in AD patients without cardiovascular disease (CVD). Mental function was measured using the MMSE at each visit, the DRS scale was also conducted but not systematically repeated. The model was adjusted for age, sex, educational level, first MMSE score, number of vascular risk factors, date of first visit, duration of disease symptoms before the study, and a propensity score. DRS = Dementia Rating Scale; MMSE = Mini-Mental Score Examination. Taken from Deschaintre, Y. (2009). Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology, 73(9), 674–680.

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ROLE OF APOE4 VS. MODIFIABLE RISK FACTORS AS PREDICTORS OF DISEASE

In the early 1990s, an important susceptibility gene for Alzheimer's disease called ApoE4 began to be mentioned (9). This gene follows an autosomal dominant inheritance pattern.

This means that if a person inherits a copy of the ApoE4 gene from one of his or her parents, his or her risk of developing Alzheimer's disease rises. We know that the highest frequency of ApoE4 gene in the world is found in Nigeria; however, paradoxically, they have the lowest rates of Alzheimer's disease, possibly due to their low cholesterol diet, and their low intake of animal fats and high intake of whole foods composed mainly of grains, roots, tubers, and vegetables (10).

This could be explained by the fact that ApoE (apolipoprotein E) plays an important role in lipid transport and metabolism, being the main cholesterol transporter protein in the brain, with ApoE4 being expressed as a genetic variant of it (11).

Notwithstanding a high prevalence of ApoE4, the incidence of Alzheimer's disease is notably low in this population group, perhaps thanks to their reduced cholesterol levels, a feat achievable for any of us through a healthy diet.

These findings suggest that long-term variations in blood cholesterol levels may have an impact on ApoE gene activity. This indicates that, despite the inheritance of genetic risk variants, we still retain the ability to modulate such factors through dietary interventions (12).

The reality is that we cannot change our genetic composition, but it is possible to reduce or prevent comorbidities. It is known that the presence of ApoE4 doubles the probability of presenting the disease, nevertheless, cholesterol and high blood pressure apparently have a greater effect when talking about prevention, control of habits and lifestyle. All this, even if the person is a carrier of the ApoE4 allele, can reduce the risk of developing the disease from an OR of 8.4 to 11 to an OR as low as 2.1(13). Regarding diet, it is a known fact that consistent adherence to a Western diet can jeopardize the health of cerebral blood vessels.

Compared to conditions such as heart attacks or strokes, prevention of Alzheimer's disease involves managing vascular risk factors such as high blood pressure and high cholesterol levels. The key lies in addressing cerebral hypoperfusion and insufficient cerebral oxygenation before the disease manifests itself. This emphasizes the importance of a healthy diet and the practice of physical and mental workout, a widely recognized but challenging knowledge to apply, and even more challenging, to pass on to our patients.

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In the setting where finding a cure for Alzheimer's and related diseases is not feasible, prevention may be the most effective strategy to buy time before experiencing significant cognitive decay. While the use of medication is a valid recommendation and can significantly improve many of the medical conditions mentioned, why not try changing habits first?

"The goal of medicine is to provide hope for patients and when there is no hope, to provide understanding. For the first time in the history of this disorder, **we have the opportunity to bring hope to these patients."**

> De la TORRE, J. C. (2002). Vascular basis of Alzheimer's pathogenesis. Annals of the New York Academy of Sciences, 977(1), 196–215.

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