Alzheimer's Disease and the Eye

Jeffrey N. Weiss

Springer

Alzheimer's Disease and the Eye

Jeffrey N. Weiss

Alzheimer's Disease and the Eye

Springer

Jeffrey N. Weiss
Parkland, FL, USA

ISBN 978-3-031-58810-5 ISBN 978-3-031-58811-2 (eBook)
https://doi.org/10.1007/978-3-031-58811-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

For the patients that have allowed us the privilege to serve.

Preface

This book is a compendium of the worldwide studies of Alzheimer's disease utilizing the eye as a biomarker, or as a treatment method, that are registered with the United States National Institutes of Health website, clinicaltrials.gov. Clinicaltrials.gov is the largest listing of research studies in the world. The presented information is accurate as of October, 2023. I have divided the studies into Recruiting, Not Yet Recruiting, Active, Not Recruiting, and Enrolling By Invitation.

In order to produce an accurate, consistent, and easy-to-read format, I corrected the mischaracterization of studies by only including those that truly belonged within each category, and corrected spelling and grammar, without changing the spirit or intentions of the submitters. The Study Title is provided, as is the Country of Origin and the Clinical Trial Number in order to make it easier for the reader to locate the study and obtain further information.

From a conceptual standpoint, early diagnosis of a clinical condition offers the potential of a better outcome. Earlier intervention is better than late intervention when the die may already be cast and progression to a negative end result can no longer be prevented.

What is meant by "early diagnosis?" How early is early? The temporal determination is related to the ability to affect the outcome. Would most people truly wish to know that in 10 years they will develop Alzheimer's disease, if there was no way to prevent it? Understandably, some might say "yes" as that knowledge would cause them to lead a healthier lifestyle, to refrain from tobacco and alcohol usage, and to exercise more. All worthy goals. But what if it also led to the person quitting their job, getting divorced, and engaging in risky activities because they felt that their fate was already sealed? And if, 10 years later, in the absence of any preventative treatment, they didn't develop the condition? Was the test just incorrect, did a change in lifestyle prevent the negative outcome, or were they just lucky? Of course, during the 10-year period a new treatment may be discovered that precludes the prior negative assured outcome.

I think most people would agree that unless there is a meaningful, successful treatment for an early diagnosis, there is no point in knowing many years in advance of the inevitable when there is little you can do to change the outcome. Lead your life and let what may come.

New drug development is costly and time consuming. If, through the use of biomarkers, study durations and research costs decrease, there is a greater possibility of a new and effective drug to treat this devastating disease. The eye offers the possibility of early diagnosis and of treatment.

I hope that by providing this reference, the field of ocular research in Alzheimer's disease will be advanced.

Parkland, FL, USA Jeffrey N. Weiss

Contents

Chapter 1
Introduction

Alzheimer's Disease

Alzheimer's disease is a progressive, degenerative brain disorder leading to death. Early-onset Alzheimer's disease (ages 30–65) is strongly related to hereditary and genetics. Late-onset Alzheimer's (age 65 and older) is the leading cause of dementia, affecting more than 5 million Americans. While associated with advancing age, there is no evidence that the disease is caused by the aging process. While particular genes may increase susceptibility to late-onset Alzheimer's, researchers are studying the effect of genetic, environmental, dietary, infectious agents, and metabolic abnormalities that may lead to disease's development.

Unfortunately, at the present time, there is no simple clinical test to diagnose this condition. Posthumously, neuritic plaques composed of amyloid protein and/or neurofibrillary tangles of tau protein are found. The average life expectancy following the diagnosis is 5–10 years. There is no successful treatment, drugs may improve symptoms in some cases.

In the last decade, more than 500 drug studies have failed to find a truly successful treatment for this condition. In the absence of a definitive quantitative endpoint, most studies have been terminated after 2 years, yet 5–10 years would have been required to determine a meaningful clinical effect.

The eye is the only place in the body where an artery, vein, and nerve can be directly visualized. The nerve fiber layer of the retina is an outgrowth of the brain. Retinal thinning is observed by noninvasive Ocular Coherence Tomography testing in patients diagnosed with Alzheimer's disease. It is apparent that a much earlier molecular effect would lead to an imaging change.

If an early, noninvasive, and cost-effective method is discovered to diagnose "early" Alzheimer's disease, then (a) pharmaceutical companies may shorten

J. N. Weiss, *Alzheimer's Disease and the Eye*,
https://doi.org/10.1007/978-3-031-58811-2_1

clinical studies, at lower research costs, leading to the development of new, effective drugs, and (b) physicians may identify patients with early disease, and prescribe the new drugs.

Rates of Dementia

Worldwide, Alzheimer's disease affects 5–8% of the general population greater than 60 years of age, or 50 million people at the present time. Sixty percent of the affected patients are in low- to middle-income countries. There are 10 million new cases per year; 82 million affected patients are projected in 2030, and 152 million in 2050.

Alzheimer's disease represents 60–70% of dementia cases, though there may be an indistinct boundary between the different types, and a patient may exhibit mixed dementia.

In 2015, the global cost of care was $818 billion US dollars, or 1.1% of the global GDP (0.2% in low- to middle-income nations to 1.4% in high-income countries).

In the United States, more than 5 million Americans are living with Alzheimer's dementia; 10% of people are older than 65 years of age and two-thirds of the patients are women. African-Americans are twice as likely as Caucasians to have Alzheimer's disease. Hispanics are 1.5× as likely as Caucasians to develop Alzheimer's. By 2050, in people age 65 and older—13.8 million of Americans will be diagnosed with Alzheimer's disease.

From 2000 to 2018 deaths from Alzheimer's increased 146%, while deaths from cardiac disease decreased by 7.8%. Sixty-one percent of 70-year-olds with Alzheimer's will die by age 80, while only 30% of 70-year-olds without Alzheimer's will die by age 80.

Seventy percent of the cost of caring for a family member with Alzheimer's is borne by families.

Twice as many Alzheimer's caregivers (compared to non-Alzheimer caregivers) report emotional, financial, and physical difficulties.

2020 US cost 305 billion (206 billion paid by Medicare/Medicaid)
2050 projected cost 1.1 trillion (in 2020 dollars)

The NIH website, www.clinicaltrials.gov, lists 470,354 research studies in the United States and in 222 other countries.

Alzheimer's disease—	2870 studies worldwide, 1503 US studies (accessed 7/14/22)
	3243 studies worldwide, 1701 US studies (accessed 10/24/23)

Biomarkers play increasingly informative roles in Alzheimer's disease trials.

Biomarkers/Clinical Endpoints

A biological marker, or biomarker, is an objective measurable indicator of a biological state, including, normal and pathologic biologic conditions, and the response to therapeutic interventions. Biomarkers are biologic molecules found in tissue, blood, or other bodily fluids. A biomarker must have validity or evaluation, that is, its effectiveness as a relevant endpoint. The biomarker must also demonstrate clinical relevance, does it provide clinically relevant information? Biomarkers are objective and quantifiable, but unlike a clinical endpoint, may not reflect the patient's well-being from their standpoint. Examples include chemistry tests, blood pressure, and pulse measurements.

The WHO definition of biomarker includes "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction."

Clinical Endpoints have traditionally been the endpoints of all medical research. They reflect the patient's health from the patient's standpoint. Patients care about how they are doing, and how they feel, not the results of an individual blood test. The old expression, "The patient died, but the lab looked good," comes into mind. Patients want treatment for their diseases and conditions, not for an abnormal laboratory result. However, the alleviation of pain or an improvement in patient symptoms may not correlate with an improvement in the clinical course.

Biomarkers may serve as interim indicators before a clinical endpoint. The appropriate biomarker should be indicative of the fundamental clinical pathway. A clinical endpoint, such as survival, may take many years to determine, whereas the biomarker may provide interim evidence about the safety and efficacy of the treatment while the definitive data are being collected. The biomarker, as a surrogate endpoint, may identify dangerous or harmful treatments before the clinical endpoint is reached. They can result in more focused, and more efficient studies, at reduced expense. The most common biomarkers utilized in Alzheimer's disease and other types of dementia are bodily fluids and neuroimaging scans. What is needed are earlier, noninvasive, and inexpensive biomarkers.

Ocular Biomarkers

The optic nerve is considered the second cranial nerve of the peripheral nervous system but technically it is part of the central nervous system and not the peripheral nervous system. The myelin covering the nerves is produced by oligodendrocytes, not the Schwann cells of the peripheral nervous system. It is formed during the seventh week of embryonic development by the diencephalon. Peripheral nerves are sheathed by epineurium, perineurium, and endoneurium, and the optic nerve is covered by meningeal layers, dura, arachnoid, and pia mater.

For this reason, the eye may be an early biomarker for Alzheimer's disease.

Retinal thinning and optic nerve atrophy have been reported in patients with Alzheimer's disease. Aβ deposition has also been observed in the lens and retina. Amyloid plaques in the retina correlate with those found in the brain. Abnormalities in tear flow rate and function have also been reported. Thus, there are multiple avenues for research in the use of the eye as a biomarker for Alzheimer's disease.

Further Reading

Armstrong RA, Syed AB. Alzheimer's disease and the eye. Ophthalmic Physiol Opt. 2008;16:S2–8. https://doi.org/10.1111/j.1475-1313.1996.95001344.x.

Ashok A, Singh N, Chaudhary S, Bellamkonda V, Kritikos AE, Wise AS, Rana N, McDonald D, Ayyagari R. Retinal degeneration and Alzheimer's disease: an evolving link. Int J Mol Sci. 2020;21(19):7290. https://doi.org/10.3390/ijms21197290. PMID: 33023198; PMCID: PMC7582766.

Cheung CY, Mok V, Foster PJ, Trucco E, Chen C, Wong TY. Retinal imaging in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2021;92(9):983–94. https://doi.org/10.1136/jnnp-2020-325347. Epub 2021 Jun 9. PMID: 34108266.

Choi SI, Lee B, Woo JH, Jeong JB, Jun I, Kim EK. APP processing and metabolism in corneal fibroblasts and epithelium as a potential biomarker for Alzheimer's disease. Exp Eye Res. 2019;182:167–74. https://doi.org/10.1016/j.exer.2019.03.012.

Crooke A, Huete-Toral F, Martı A, Colligris B, Pintor J. Ocular disorders and the utility of animal models in the discovery of melatoninergic drugs with therapeutic potential. Expert Opin Drug Discov. 2012;7:989–1001. https://doi.org/10.1517/17460441.2012.714769.

Dutescu RM, Li QX, Crowston J, Masters CL, Baird PN, Culvenor JG. Amyloid precursor protein processing and retinal pathology in mouse models of Alzheimer's disease. Graefes Arch Clin Exp Ophthalmol. 2009;247:1213–21. https://doi.org/10.1007/s00417-009-1060-3.

Goldstein LE, Muffat JA, Cherny RA, Moir RD, Ericsson MH, Huang X, Mavros C, Coccia JA, Faget KY, Fitch KA, et al. Cytosolic β-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. Lancet. 2003;361:1258–65. https://doi.org/10.1016/S0140-6736(03)12981-9.

Kalló G, Emri M, Varga Z, Ujhelyi B, Tozsér J, Csutak A, Csosz É. Changes in the chemical barrier composition of tears in Alzheimer's disease reveal potential tear diagnostic biomarkers. PLoS One. 2016;11:1–14. https://doi.org/10.1371/journal.pone.0158000.

Kerbage C, Sadowsky CH, Tariot PN, Agronin M, Alva G, Turner FD, Nilan D, Cameron A, Cagle GD, Hartung PD. Detection of amyloid β signature in the lens and its correlation in the brain to aid in the diagnosis of Alzheimer's disease. Am J Alzheimers Dis Other Dement. 2015;30:738–45. https://doi.org/10.1177/1533317513520214.

Klyucherev TO, Olszewski P, Shalimova AA, Chubarev VN, Tarasov VV, Attwood MM, Syvänen S, Schiöth HB. Advances in the development of new biomarkers for Alzheimer's disease. Transl Neurodegener. 2022;11(1):25. https://doi.org/10.1186/s40035-022-00296-z. PMID: 35449079; PMCID: PMC9027827.

Koronyo Y, Rentsendorj A, Mirzaei N, Regis GC, Sheyn J, Shi H, Barron E, Cook-Wiens G, Rodriguez AR, Medeiros R, Paulo JA, Gupta VB, Kramerov AA, Ljubimov AV, Van Eyk JE, Graham SL, Gupta VK, Ringman JM, Hinton DR, Miller CA, Black KL, Cattaneo A, Meli G, Mirzaei M, Fuchs DT, Koronyo-Hamaoui M. Retinal pathological features and proteome signatures of Alzheimer's disease. Acta Neuropathol. 2023;145(4):409–38. https://doi.org/10.1007/s00401-023-02548-2. Epub 2023 Feb 11. PMID: 36773106; PMCID: PMC10020290.

Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL. Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. NeuroImage. 2011;54:S204–17. https://doi.org/10.1016/j.neuroimage.2010.06.020.

More SS, Vince R. Hyperspectral imaging signatures detect amyloidopathy in Alzheimers mouse retina well before onset of cognitive decline. ACS Chem Neurosci. 2015;6:306–15. https://doi.org/10.1021/cn500242z.

Ning A, Cui J, To E, Ashe KH, Matsubara J. Amyloid-β deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Investig Ophthalmol Vis Sci. 2008;49:5136–43. https://doi.org/10.1167/iovs.08-1849.

Örnek N, Dag E, Örnek K. Corneal sensitivity and tear function in neurodegenerative diseases. Curr Eye Res. 2015;40:423–8. https://doi.org/10.3109/02713683.2014.930154.

Romaus-Sanjurjo D, Regueiro U, López-López M, Vázquez-Vázquez L, Ouro A, Lema I, Sobrino T. Alzheimer's disease seen through the eye: ocular alterations and neurodegeneration. Int J Mol Sci. 2022;23(5):2486. https://doi.org/10.3390/ijms23052486. PMID: 35269629; PMCID: PMC8910735.

Singh AK, Verma S. Use of ocular biomarkers as a potential tool for early diagnosis of Alzheimer's disease. Indian J Ophthalmol. 2020;68:555–61.

Snyder PJ, Alber J, Alt C, Bain LJ, Bouma BE, Bouwman FH, DeBuc DC, Campbell MCW, Carrillo MC, Chew EY, Cordeiro MF, Dueñas MR, Fernández BM, Koronyo-Hamaoui M, La Morgia C, Carare RO, Sadda SR, van Wijngaarden P, Snyder HM. Retinal imaging in Alzheimer's and neurodegenerative diseases. Alzheimers Dement. 2021;17(1):103–11. https://doi.org/10.1002/alz.12179. Epub 2020 Oct 8. PMID: 33090722; PMCID: PMC8062064.

van Wijngaarden P, Hadoux X, Alwan M, Keel S, Dirani M. Emerging ocular biomarkers of Alzheimer disease. Clin Exp Ophthalmol. 2017;45:54–61. https://doi.org/10.1111/ceo.12872.

Zhang J, Shi L, Shen Y. The retina: a window in which to view the pathogenesis of Alzheimer's disease. Ageing Res Rev. 2022;77:101590. https://doi.org/10.1016/j.arr.2022.101590. Epub 2022 Feb 19. PMID: 35192959.