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The WCC Note™

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Alzheimer's: Who Gets It — and Why?

Charlton Heston, actor. Rita Hayworth, actress. John F. Riordan, mathematician and engineer who specialized in combinational mathematics. Tom O'Horgan, Director of the Broadway musical "Hair." William W. Kaufmann, "a close adviser to seven defense secretaries and a major proponent of a shift away from the early Cold War strategy of mass nuclear retaliation against the Soviet Union." Jack Cover, physicist who invented the Taser stun gun. Hewitt D. Crane, who helped create the first commercial computer to automate checking accounts. Sammy Baugh, great National Football League quarterback. C. Lester Hogan, a pioneer in the electronics industry. Arthur Hill, actor who won a Tony Award in "Who's Afraid of Virginia Woolf?" Donald Finkel, noted American poet. Dr. William B. Schwartz, "a leading health economist whose studies of the effects of market forces on medicine led him to predict that unbridled costs could lead to a rationing of care." Charles Morgan, Jr., civil rights lawyer. Rear Admiral Eugene B. Fluckey, "one of America's most daring submarine commanders of World War II." Milton Jerrold Shapp, former Governor of Pennsylvania.

All these people died with Alzheimer's disease (AD), according to their *New York Times* obituaries. Alzheimer's does not discriminate. It ravages the very essence of our humanity – our memories. From a former president to the neighbor next door, it plays a roulette game with our lives.

This issue of **The WCC Note** *begins with a review of recent literature on Alzheimer's, starting with what we know about its pathology and genetics. Upcoming issues will address its diagnosis, biomarkers, treatment, and prevention, and the status of imaging's very important role.*

WHO GETS IT?

Who Gets Alzheimer's?

The National Institute on Aging estimates between 2.4 to 4.5 million Americans (2) and more than 20 to 37 million people worldwide (3, 4) currently live with AD. Reports predict a United States prevalence of 8.64 million (range: 4.37-15.4 million) by the year 2047. (5)

The percent of people with AD doubles about every five years of age, beginning with roughly 1 percent of those age 60 and reaching 40 percent or more of those 85 years old. Research estimates 5% to 10% of cases are familial, most being sporadic. (6)

ALZHEIMER'S AND GENETICS

What Do We Know about Alzheimer's Genetics?

While AD typically afflicts the elderly after age 60, a small subset of patients, roughly 5 percent, develops it at a younger age – from their thirties through their fifties (2, 7), and in rare cases as early as their twenties. (8) The genetic basis of the disease remains under continued scrutiny, but research has established several known links, which differ between these two groups.

Early-onset AD genetics: A mutation in one of three inherited genes carries the risk of AD. (2, 7) These mutations result in formation of abnormal proteins and are autosomal-dominant.

a. *Chromosome 21:* Causes abnormal amyloid precursor protein (APP). The Aβ peptide which accumulates in AD is cleaved from APP, the gene for which resides on chromosome 21. People with Trisomy 21 (Down's syndrome) sustain the brain pathology of AD. (8)

b. *Chromosome 14:* Causes abnormal presenilin 1.

c. *Chromosome 1:* Causes abnormal presenilin 2.

Late-onset AD genetics: The mutations found in early-onset AD do not carry association with late-onset AD. No signature genetic link to late-onset AD has been identified, but genetic risk factors appear to be present. Such genetic risk factors are variants in cellular DNA that increase disease likelihood, but do not directly cause the disease. A genetic profile related to apolipoprotein E (APOE) increases likelihood of AD. APOE encodes instructions for a cholesterol transport protein, and APOE exists in several alleles (or forms). One of these alleles is APOE ε4.

Genetic risks in late-onset AD include:

a. *APOE ε4*: About 40 percent of AD patients carry the APOE ε4 form of the gene APOE, though not everyone with APOE ε4 gets AD, and many people with AD do not carry the APOE ε4 allele. (2, 7)

b. *SORL1:* Discovered in 2007, it may be another genetic association and is involved with APP transport within cells. (2, 7)

c. *CALHM1:* This appears to be involved in calcium homeostasis. (9, 10)

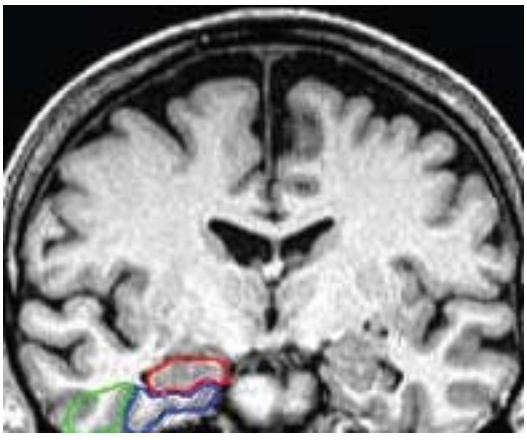
d. *PCDH11X:* A single nucleotide polymorphism in this X-linked gene is the first sex-specific risk factor found. (11, 12)

e. *Other AD genetic risk factors* may exist. The ongoing genome-wide association study (GWAS) employs rapidly scanning markers in complete DNA sets to assess for genetic variations that may associate with AD. (13)

BRAIN PATHOLOGY

What Is the Pathology of Alzheimer's?

Macroscopically, the brain in AD demonstrates cortical atrophy, which is most severe in the frontal, temporal, and parietal lobes. (13) Microscopically, neuritic (senile) plaques, neurofibrillary tangles, and amyloid angiopathy occur — all of which can happen to a lesser degree with normal aging. The pathologic plaques and tangles, and ensuing neuronal loss and glial reactions, start first in the entorhinal cortex, move on to the hippocampal formation and isocortex, and then to the neocortex. (13)



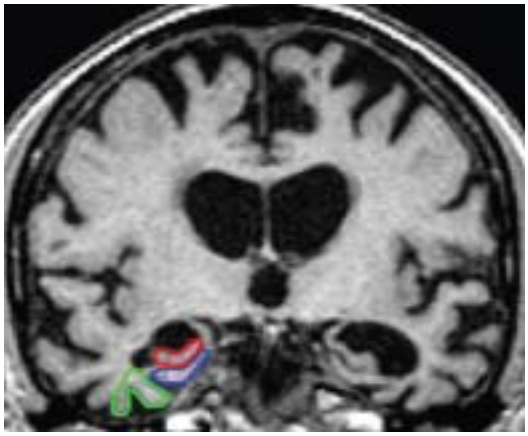
The normal MRI brain scan above, showing no atrophy, depicts the three areas of interest in the brain's medial temporal lobe: hippocampus (outlined in red); entorhinal cortex (blue) and perirhinal cortex (green). (30)

1. **Amyloid:** For years, research has linked AD to accumulation of amyloid β peptides (Aβ). These peptides first form short chains, called oligomers, that are thought to be toxic and make long, sticky fibrils that create brain plaques. (14) Subsequent neuronal cell dysfunction and death ensue, accompanied by deficient neurotransmitters. (15)

    a. *Neuritic plaques* often contain central amyloid (amyloid β in dominance), with microglial cells and reactive astrocytes peripherally. Other plaque proteins include complement components, proinflammatory cytokines, alpha1-antichymotrypsin, and apolipoproteins. (6)

b. *Neurofibrillary tangles:* Inside neurons, these consist of an insoluble protein called tau. (17) The Aβ peptides become cleaved from the amyloid precursor proteins (APP) by γ-secretase and β -secretase enzymes. (The function of APP is unknown.) The toxic Aβ peptides get taken up and released by plaques, stressing cells and creating so much phosphorylation of tau that it tangles. (17)

c. *Cerebral amyloid angiopathy* almost always occurs in AD, but also can occur in people without the disease. (6)



The MRI scan above shows severe atrophy indicative of Alzheimer's pathology in all areas except the right perirhinal cortex, which has moderate atrophy. (30)

2. **Role of astrocytes:** Reports theorize that atrophy of astroglia and reactive hypertrophic astrogliosis both may occur in dementia. (16) Astrocytes comprise the most numerous brain cell type. To review their function, they are glial cells believed to participate in metabolic buffering or detoxifying, nutrient supply, electrical insulation, barrier functions, repair, and scar formation. (13)
3. **Other features:** These include granulovacuolar degeneration, most commonly occurring in the hippocampus and olfactory bulb; and Hirano bodies, most commonly in hippocampal pyramidal cells. (6) Of note, the symptom of decreased sense of smell can be a harbinger complaint of AD. (2)

Does the pathology cause immediate symptoms?

No. A subclinical, asymptomatic state of AD brain damage with tangle and plaque formation occurs in people for up to ten to 20 years. (2)

AMYLOID AND ALZHEIMER'S

How Does Amyloid β Cause AD?

This is a complex and compelling question; two recent studies attempt to tackle it. One found that amyloid β may disrupt mitochondrial function (18, 19). Another study looked at the production of Aβ pyroglutamate (pE)-modified peptides. These are peptides prone to aggregate that are created by the enzyme glutaminyl cyclase. Both these peptides and this enzyme are upregulated in Alzheimer's patients as compared to controls. (18, 20)

CAUSES

Why Does AD Happen?

Attempting to solve this labyrinthine problem, researchers speculate that, in the general population, predisposing genetic risks and environmental factors interact with physiological brain aging processes to cause AD.

Some of the proposed nongenetic risks include toxins, viruses, prions, a low level of education, and head trauma. (8) Controversy accompanies studies related to traumatic head injury, hypercholesterolemia and high- and low-density lipoprotein fractions, elevated serum homocysteine, and vitamin E. (21)

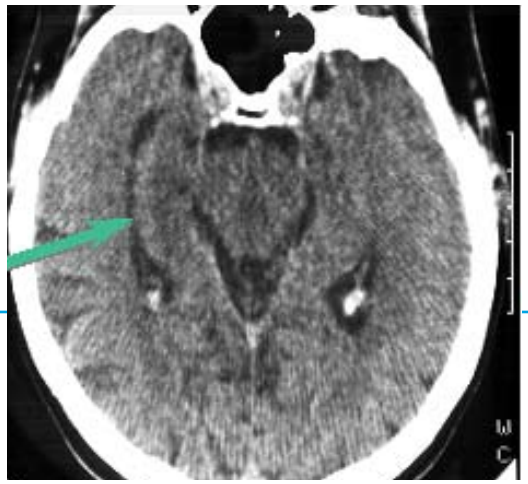
Regular light alcohol use, especially of wine, may decrease AD. (22, 23) This may relate to grapeseed polyphenols (24), which have been shown to inhibit amyloid β-protein aggregation into high-molecular-weight oligomers *in vitro.*(25) However, heavy drinking (more than two drinks a day) and smoking may increase risk, according to a report from the American Academy of Neurology meeting. (26)

Diabetes Type 2 and AD may be linked, since insulin influences the metabolism of beta-amyloid precursor protein (APP) in neurons, decreasing the intracellular accumulation of Aβ peptides. This carries implications for oral hypoglycemic agents. (27)

EARLY DIAGNOSIS

Would Early Diagnosis Make a Difference?

Trials to assess therapeutic intervention in AD have included patients with advanced disease, people whose brains may have already sustained irreversible damage. (17) Diagnosing the disease *before* irreparable brain damage would allow assessment of a therapy's true ability to allay symptoms.



The brain MRI above shows the state of the medial temporal lobe (green arrow) at the time of Alzheimer's symptom presentation. (31)

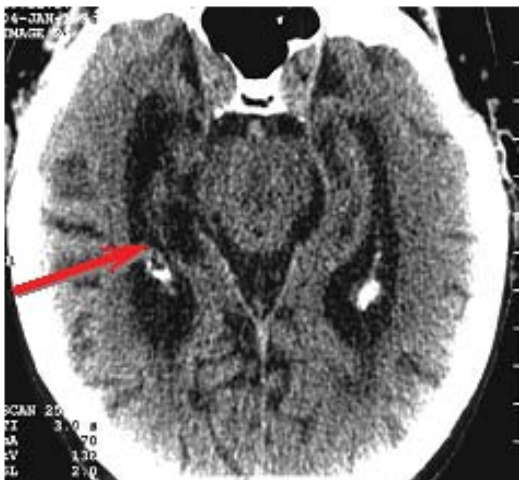
PRIONS AND ALZHEIMER'S

"Mad Cow" Disease Is Linked to Prions; What Do They Have to Do with Alzheimer's?

Recent literature reports non-infectious prion proteins may be a mediator in the development of AD. (3, 14, 28) The brain produces normal prion proteins, but these can result in disease if they contact an infections form called PrP^{Sc}. (14) The normal prion protein in cellular form (PrP^{C}) anchors to the cell membrane and helps maintain brain white matter. A misfolded, clumped, and very pathogenic form of infectious prion protein, called PrP^{Sc}, causes Creutzfeldt-Jakob and "Mad Cow" diseases.

The function of normal brain prions is unknown, but recently a study found that they may be needed for mice to possess a normal sense of smell. (29)

Amyloid-β oligomers interact with neuronal membrane prion protein, which may impair the signaling pathway needed for synaptic plasticity important in learning and memory. Alternatively, internalization of the prion protein PrP^{C} may let the amyloid-β oligomers into the cell, where they might disrupt cell functions. (3)



The MRI above, acquired seven years after the previous scan, shows rapid atrophy of the same area (red arrow) as a result of AD. (31)

CONCLUSION

CONCLUSION: A global, common, and tyrannical disease, Alzheimer's displays a multifactorial risk profile of genetic and nongenetic causes and a link to amyloid — all factors that are undergoing continued investigation.

For more information on this or any other clinical trial imaging topic, please e-mail newsletter@wcclinical.com or call our Clinical Trial Imaging Hotline: 1-617-250-5143

Next Issue: More on Alzheimer's and Imaging

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