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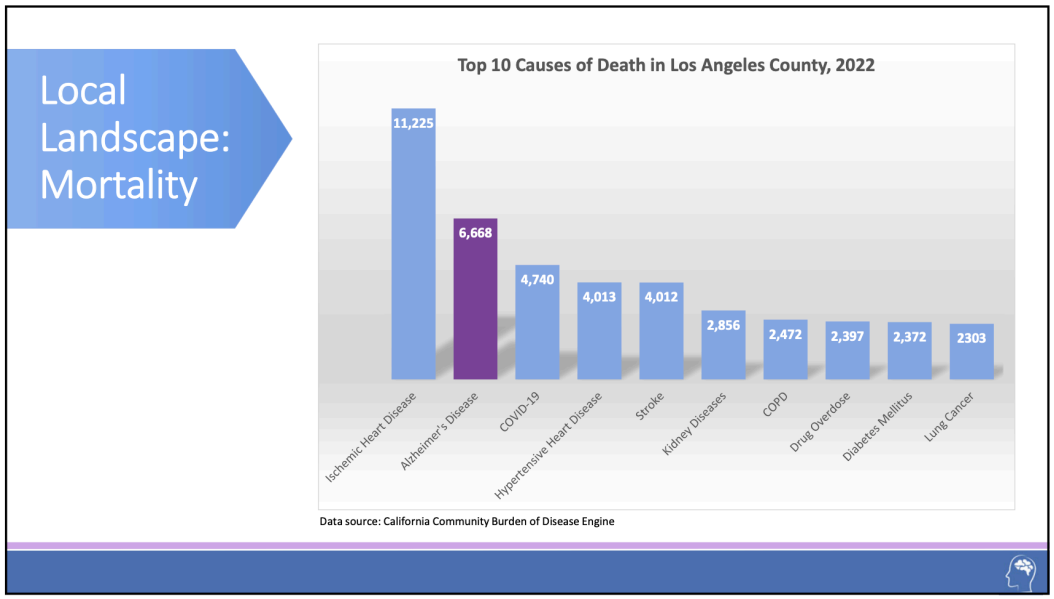
Alzheimer's - An Upcoming Epidemic

There is a tsunami coming. Not a tsunami from the sea, but a healthcare tsunami of Alzheimer's patients. For every patient officially diagnosed with Alzheimer's disease, many more are living with this condition undiagnosed.

1. Alzheimer's disease is currently the 6th leading cause of death in the United States. It is projected to become the 4th leading cause of death by the year 2030.
2. More than 6.7 million Americans are estimated to have Alzheimer's in the United States. This number is expected to triple by the year 2050.
3. While death rates from heart attacks, strokes, and cancer have been decreasing due to advancing treatments and prevention – the number of deaths from Alzheimer's has increased over 100% in the last 10 years.
4. This disease costs the nation over $200 billion in 2017. That rate is expected to rise to $1.2 trillion by the year 2050.
5. It is common to hear about people who have survived heart attacks, strokes, and cancer – however there are no survivors of Alzheimer's disease.



“Plaques and Tangles”

Formation of an “Amyloid Plaque”

1. Amyloid Precursor Protein (APP):
    - Amyloid precursor protein (APP) is a large protein found in neuron cell membranes. It is a normal component of the cell membrane. A combination of genetics, environment, and lifestyle factors initiate the splicing of APP into Beta Amyloid peptides.
2. Formation of Amyloid Monomer:
    - Initially, APP undergoes processing, resulting in the release of amyloid-beta (Aβ) peptides. These peptides start as individual molecules known as monomers.
3. Aggregation into Amyloid Dimers and Oligomers:
    - Due to their structure, Aβ monomers have a tendency to cluster together, forming small groups called dimers (pairs of Aβ monomers) and then oligomers (multiple Aβ monomers grouped together).
4. Maturation into Protofibrils and Plaques:
    - Over time, these oligomers further assemble into protofibrils, elongated structures that can eventually mature into insoluble beta-amyloid plaques. These plaques are characteristic of Alzheimer's disease.

Amyloid plaques play a significant role in the development and progression of Alzheimer's disease. Here's a detailed discussion about their role:

1. Formation of Amyloid Plaques:
    - Amyloid plaques are clumps of beta-amyloid protein fragments that accumulate between nerve cells (neurons) in the brain.
    - Beta-amyloid is a naturally occurring protein in the brain. However, in Alzheimer's disease, these proteins are not properly broken down and cleared, leading to their accumulation and the formation of plaques.

2. Impact on Neuronal Function:
    - Amyloid plaques disrupt the communication between neurons. They interfere with the synapses, which are the connections through which neurons communicate by sending and receiving signals.
    - This disruption affects the transmission of electrical impulses and the release of neurotransmitters, which are crucial for normal brain function, including learning and memory.

3. Neurotoxic Effects:
    - Accumulated beta-amyloid can trigger a series of harmful processes that contribute to neuronal damage and death.
    - Neurotoxic effects of amyloid plaques include inflammation in the brain, oxidative stress (damage caused by free radicals), and the activation of immune cells that can further damage neurons.

4. Tau Protein Interaction:
    - Amyloid plaques are often associated with another hallmark feature of Alzheimer's disease: neurofibrillary tangles composed of tau protein.
    - Tau proteins help maintain the structure and stability of neurons. However, in Alzheimer's disease, abnormal tau proteins form tangles inside neurons, leading to structural damage and neuronal dysfunction.
    - The interaction between amyloid plaques and tau tangles is complex and contributes to the progression of cognitive decline and neurodegeneration in Alzheimer's.

5. Role in Disease Progression:
    - The presence of amyloid plaques is one of the key pathological hallmarks used in diagnosing Alzheimer's disease, alongside tau tangles and neuronal loss.
    - While amyloid plaques may develop years before symptoms appear (as seen in the pre-clinical stage), their accumulation is believed to contribute to the progressive cognitive decline observed in clinical Alzheimer's disease.

    - Over time, the burden of amyloid plaques and their neurotoxic effects can lead to widespread brain damage, affecting multiple cognitive functions and ultimately resulting in the characteristic symptoms of Alzheimer's, such as memory loss, language difficulties, and impaired reasoning.

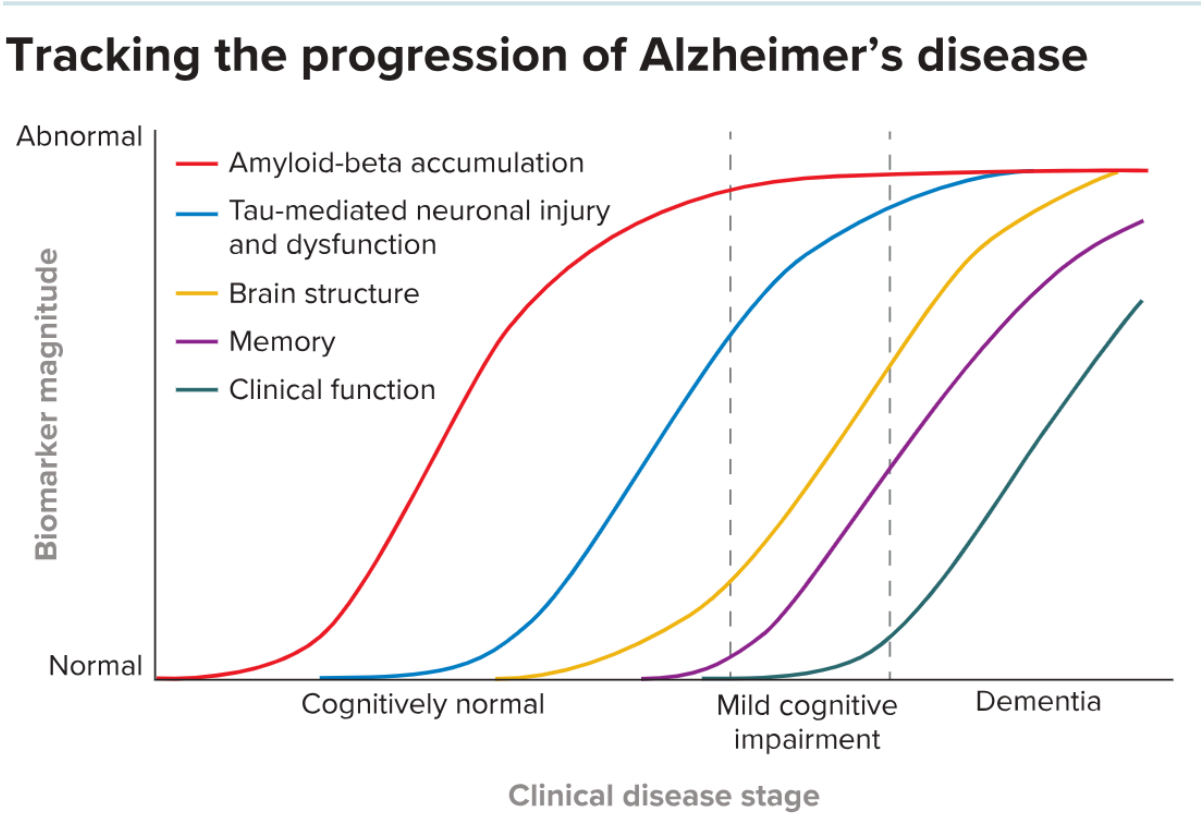
“Oligomers and Protofibrils”

1. Amyloid Oligomers:
    - Amyloid oligomers are intermediate forms of beta-amyloid that exist between individual beta-amyloid molecules and fully formed amyloid fibrils (plaques).
    - These oligomers are highly toxic to neurons and are believed to contribute significantly to synaptic dysfunction and neuronal damage in Alzheimer's disease.

- Amyloid oligomers can disrupt synaptic function by interfering with neurotransmitter release and receptor activity, leading to impaired neuronal communication and synaptic plasticity.
- Their small size allows them to easily spread and interact with multiple targets, exacerbating their neurotoxic effects and contributing to the progressive cognitive decline observed in Alzheimer's.

2. Protofibrils:
    - Protofibrils are larger and more structured assemblies of beta-amyloid than oligomers but are smaller and less dense than mature amyloid fibrils (plaques).
    - Similar to amyloid oligomers, protofibrils exhibit neurotoxic properties and can disrupt synaptic function and neuronal integrity.
    - Protofibrils can directly interact with cell membranes, disrupting their stability and leading to calcium dysregulation and oxidative stress within neurons.
    - Their ability to form pores in cell membranes can disrupt ion homeostasis and trigger apoptotic pathways, contributing to neuronal death and the progression of Alzheimer's pathology.

3. Role in Disease Progression:
    - Both amyloid oligomers and protofibrils are implicated in the early stages of Alzheimer's disease, often appearing before the formation of amyloid plaques.
    - Their neurotoxic effects contribute to synaptic dysfunction, neuronal injury, and the loss of synaptic connections, which are central features of Alzheimer's-related cognitive decline.
    - The accumulation and aggregation of amyloid oligomers and protofibrils are thought to initiate a cascade of pathological events, including inflammation, oxidative stress, and tau protein abnormalities, ultimately leading to widespread neurodegeneration and the clinical manifestations of Alzheimer's disease.



Research suggests that different biomarkers correspond with different phases of Alzheimer’s disease. First amyloid begins to accumulate, then tau. Neurodegeneration causes memory loss and other symptoms as the disease progresses.

Alzheimer's disease is often categorized into three stages: pre-clinical, mild cognitive impairment (MCI), and clinical Alzheimer's disease. These stages help clinicians understand the progression of the disease and tailor interventions accordingly.

1. Pre-Clinical Stage (up to 20 years before symptoms of memory loss)
    - Description: This stage occurs before noticeable symptoms appear. Individuals in the pre-clinical stage may have underlying brain changes associated with Alzheimer's, such as the accumulation of beta-amyloid plaques and tau tangles, but they do not yet show significant cognitive or functional decline.
    - Characteristics:
        - No apparent symptoms or subtle changes that are not noticeable in daily life.

        - Brain changes are detectable through advanced imaging techniques or biomarker analysis.
        - Individuals may be functioning normally in terms of memory, thinking, and daily activities.
2. Mild Cognitive Impairment (MCI):
    - Description: MCI is often considered an intermediate stage between normal age-related cognitive changes and dementia. Not all individuals with MCI progress to Alzheimer's disease, but it is considered a risk factor.
    - Characteristics:
        - Noticeable changes in cognition, such as memory lapses, difficulty finding words, or challenges with problem-solving, that are noticeable to the individual and sometimes to others.
        - These cognitive changes are beyond what is expected for a person's age but do not significantly impair daily functioning or independence.
        - Individuals with MCI may still be able to perform routine tasks and maintain social relationships, although they may require more effort or assistance.
3. Clinical Alzheimer's Disease:
    - Description: This stage represents the full manifestation of Alzheimer's disease, characterized by significant cognitive and functional decline that interferes with daily life.
    - Characteristics:
        - Memory loss that disrupts daily activities, such as forgetting recent events, repeating questions, or relying heavily on memory aids.
        - Challenges with language and communication, including difficulty finding words, following conversations, or expressing thoughts.
        - Impaired judgment, decision-making, and problem-solving abilities.
        - Disorientation to time, place, and familiar surroundings.
        - Changes in mood, behavior, and personality, which may include mood swings, agitation, withdrawal, or depression.
        - Gradual loss of independence in activities of daily living (ADLs), such as bathing, dressing, cooking, and managing finances.
        - Progressive decline in cognitive function over time, leading to severe impairment in later stages.

It's important to note that the progression through these stages can vary widely among individuals. Some may remain stable in one stage for a prolonged period, while others may progress more rapidly. Early detection, diagnosis, and appropriate management can help improve quality of life and support individuals and their caregivers throughout the course of the disease.

Diagnostic Tests - Brain Scans, CSF Fluid, and Blood-Based Biomarkers

Brain Scans:

FDA approved Amyloid and Tau PET scans can detect the presence of both beta amyloid plaque and neurofibrillary tau tangle changes in the brain associated with Alzheimer's disease.

CSF Fluid Diagnosis:

Analyzing the CSF fluid for the presence of amyloid beta and tau proteins can provide valuable insights into Alzheimer's disease progression. Elevated levels of these biomarkers in the CSF are associated with the development and progression of Alzheimer's pathology.

Blood-Based Biomarkers:

Advancements in medical technology have led to the development of blood-based biomarkers for Alzheimer's disease. Blood tests that detect levels of amyloid and tau proteins are becoming increasingly reliable tools for early diagnosis and monitoring of Alzheimer's progression.

Combining Brain Scans and Biomarkers:

Integrating PET brain scans with blood-based biomarkers enhances the accuracy of Alzheimer's diagnosis. This multi-modal approach allows healthcare professionals to assess structural changes in the brain alongside biochemical markers associated with Alzheimer's pathology.

Current FDA Approved Medications and Emerging Treatments

FDA Approved Medications:
As of the latest update, there are five FDA-approved medications for Alzheimer's disease aimed at supporting brain communication processes:

1. Donepezil (Aricept) - approved in 1996
2. Rivastigmine (Exelon) - approved in 2000
3. Galantamine (Razadyne) - approved in 2001
4. Memantine (Namenda) - approved in 2003
5. Lecanemab (Leqembi) - approved 2023

A recent milestone in Alzheimer's treatment is the FDA approval of Leqembi, a monoclonal antibody designed to clear beta-amyloid plaque in the brain. Leqembi represents a significant advancement in addressing the underlying pathology of Alzheimer's disease by targeting the accumulation of beta-amyloid, a hallmark feature of the condition.

Three Buckets of Alzheimer’s Causes

1. Circulation

Any condition that causes poor circulation to the body will increase the risk of having Alzheimer’s disease.
Statistics show that out of every 10 patients with Alzheimer’s:

- Eight have hypertension (high blood pressure).
- Four have diabetes.
- Three have heart disease.

Many have high cholesterol, obesity, and poor physical fitness.

- Any condition that is a risk factor for heart disease is also a risk factor for Alzheimer’s disease.

2. Inflammation

Inflammation conditions can affect any organ system of your body. When inflammation becomes chronic, it increases the risk of Alzheimer’s.
Organ system inflammation and associated pathologic diagnosis:

- Brain – Alzheimer’s disease (high number of inflammatory cells found in brains of Alzheimer’s patients at autopsies).

3. Toxins

Toxins can come from the air as well as food and water.
Research shows that those who live in areas of high pollution have a higher risk of Alzheimer’s diagnosis compared to those who live in areas of low pollution.
Toxins can come from your diet as well. If you eat meat, you are not just eating an animal. You are also consuming:

1. Hormones injected into farm animals and poultry to speed up growth for faster corporate profits.
2. Antibiotics given to meat and dairy animals to prevent infections.
3. Anything that was fed to the cow – including parts of other cows.

Risk Reduction Strategies – 8 Pillars

1. Physical Exercise
2. Brain Exercise
3. Nutrition
4. Adequate Sleep
5. Social Engagement
6. Control of medical conditions
7. Stress reduction/mental health
8. Clinical trial participation

Pillar 1 - Physical Exercise

Physical exercise of at least 30-minutes a day has been shown to help both the heart and the brain.

1. Physical exercise does not have to be stringent like running, jogging, or bicycling. A nice brisk walk of 30-minutes a day would be adequate.
2. For those who cannot exercise 30-minutes a day, consider doing 15-minutes of exercise twice a day, or 10-minutes of exercise three times a day.
3. Exercise improves blood circulation – which addresses the Circulation Bucket of Causes.
4. Exercise has been shown in clinical studies to decrease the risk of Alzheimer's diagnosis, and for those who do get diagnosed, exercise delays the time till onset of symptoms.
5. Exercise can come in a variety of forms: Balance, Flexibility (stretching), Aerobic endurance, Strength Training.

Pillar 2 - Brain Exercise

Your brain cells can still make new connections with learning at any age. When you challenge your brain to think and learn, you apply the "use it or lose it" concept – use the brain and keep it healthy, or don't use the brain and "lose it" over time. Some tips on brain exercises:

1. Choose activities that challenge your mind.
2. Learn new skills.

3. Engage multiple senses such as learning to cook a new recipe (smell, taste, sight, sound).
4. Engage your brain in different ways at the same time – socializing, fine-motor skills, learning and applying new information.

Pillar 3 - Nutrition

Mediterranean Diet. This diet published in clinical research has consistently shown to reduce Alzheimer's risk.

1. Green leafy vegetables: spinach, salad greens, etc. At least six servings per week.
2. Other vegetables. At least daily.
3. Nuts: almonds, walnuts, pistachios, etc. At least five servings per week.
4. Berries: blackberry, blueberry, raspberry, etc. At least two servings per week.
5. Beans: black bean, pinto bean, refried bean. At least three servings per week.
6. Whole grain: emphasis is on "whole" which is fiber. At least three servings per day.
7. Fish: At least once a week.
8. Poultry: Chicken or turkey. At least twice a week.
9. Olive Oil: use for salads and main cooking oil.

Pillar 4 - Adequate Sleep

Good Sleep is needed for good health. Here is how sleep affects the body:

1. Immune system is weakened if sleep deprived. (Sleep deprivation increases the risk of cold or flu).
2. Tissue healing occurs during sleep (improved wound healing).
3. Pain control improves with sleep.
4. Cardiovascular health – Increase heart disease associated with lack of sleep (less than five hours at night).
5. Reaction time is impaired with poor sleep (increase risk for car accidents).
6. Balance is poor with lack of sleep (increase risk of falls).
7. Cognitive brain function is poor with lack of sleep (sleep allows memories to form and consolidate).

Pillar 5 - Social Engagement

Staying socially active and maintaining relationships can help promote physical, emotional, and brain health.

Benefits of Social Engagement:

1. Reduce risk for heart problems, osteoporosis, diabetes, and arthritis.
2. Reduce risk for mental health issues such as depression.
3. Increase opportunities for more physical exercise.
4. Protect against illness by boosting the immune system.
5. May reduce the risk for Alzheimer’s disease.

Pillar 6 - Control of Medical Conditions

Medical Conditions Associated with Poor Brain Health:

1. Heart disease
2. Diabetes
3. High Blood Pressure
4. Obesity
5. High Cholesterol
6. Elevated Homocysteine
7. Depression
8. Low Vitamin D, B6, B12, Folate, A, C, E

Pillar 7 - Stress Reduction/Mental Health

1. Stress Management Techniques: Mindfulness meditation, deep breathing exercises, yoga, and progressive muscle relaxation to help manage stress levels.
2. Importance of Mental Well-being: Discuss the link between mental health and cognitive function, emphasizing the role of stress reduction in promoting brain health and potentially reducing Alzheimer's risk.
3. Social Support Networks: Maintain strong social connections and seeking support from friends, family, or support groups for managing stress and improving mental well-being.

Pillar 8 - Clinical Trials Participation

1. Benefits of Clinical Trials: Participation in Alzheimer's clinical trials can contribute to advancing research, developing new treatments, and improving patient outcomes.
2. Finding Clinical Trials: Provide information on resources or websites where individuals can find ongoing clinical trials related to Alzheimer's disease and cognitive health.
3. Informed Consent and Safety: Understand the informed consent process, potential risks, and benefits before participating in a clinical trial. Highlight safety measures and ethical considerations in research.