A SURVEY ON ALZHEIMER’S DISEASE

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ABSTRACT:

Alzheimer’s disease (AD) is one of the most common neurodegenerative diseases and is considered to be the main cause of cognitive impairment in elderly people. The major symptom of AD is progressive dementia that eventually results in dysfunction of daily life. Due to the fact that AD has a long period of incubation before clinical symptoms emerge, the available therapeutic treatments can only improve the symptoms but not delay the progression of AD. Therefore, there is an urgent need to explore effective diagnostic approaches to catch and better treat the disease before clinical symptoms appear. Alzheimer's disease (AD) is the most common form of Dementia among older people. Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. AD begins slowly. It first involves the parts of the brain that control thought, memory and language. People with AD may have trouble remembering things that happened recently or names of people they know. A related problem, mild cognitive impairment (MCI), causes more memory problems than normal for people of the same age. Many, but not all, people with MCI will develop AD. In AD, over time, symptoms get worse. People may not recognize family members. They may have trouble speaking, reading or writing. They may forget how to brush their teeth or comb their hair. Later on, they may become anxious or aggressive, or wander away from home. Eventually, they need total care. This can cause great stress for family members who must care for them. AD usually begins after age 60. The risk goes up as you get older. Your risk is also higher if a family member has had the disease. No treatment can stop the disease. However, some drugs may help keep symptoms from getting worse for a limited time.

KEYWORDS: Alzheimer’s disease (AD), Dementia, Alois Alzheimer and Auguste D, peculiar disease of the cerebral cortex, Acetylcholinesterase inhibitors: rivastigmine And galantamine. Memantine, NMDA (glutamate) receptor antagonists, secretase (protease) enzymes, Mild Cognitive Impairment (MCI),
INTRODUCTION:

Alzheimer’s disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks.

ALZHEIMER’S DISEASE:

Alois Alzheimer Auguste D:

The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a ‘peculiar disease of the cerebral cortex,’ who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.1-3 Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD.

Epidemiology Of AD:

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after age 65. The vast majority of individuals suffering from AD are aged 65 or older and have ‘late-onset’ or ‘sporadic’ AD (~95% of all cases). Rare genetic mutations are associated with the development of AD before age 65, which is known as ‘early onset’ or ‘familial’ AD (B5% of all cases). People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down’s syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD. The prevalence of AD is higher among females, reflecting the longer life expectancy of women. Lower educational attainment has been associated with increased risk of AD dementia, consistent with the idea that education serves to increase a person’s cognitive reserve and resilience to AD pathology. A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the development and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.
Symptoms of AD:

- Memory loss
- Gradual loss of ability to perform normal tasks
- Loss of vision and coordination
- Inability to recognize and use familiar objects
- Challenges in planning or solving problems
- Confusing day from night
- Inappropriate use of words
- Mood changes

Neuropathology of AD:

- plaques
- neurofibrillary tangles (nft) (tau)
- nerve cell and synapse dysfunction, loss of connections, cell death, brain shrinkage
- Inflammation.

Alzheimer’s disease Neuroimaging Initiative (ADNI):
New Proposed Criteria:

A/T/N Classification:

➢ strictly based on 3 binary (yes/no, +/-) biological markers

- A: Amyloid Biomarker - Amyloid PET or CSF Aβ42
- T: Tau pathology biomarker - CSF p-tau or tau PET
- N: Quantitative or topographic biomarker of neurodegeneration or neuronal injury (CSF t-tau, FDG-PET, structural MRI)

- Example: A+/ T+/ N+

Risk Issues & Genetics:

➢ You Are At Higher Risk of Alzheimer’s disease If………

- Are Over The Age Of 65
- Have Had A Serious Head Injury, Particularly Repeated Injuries
- Have Genes That Are Involved With The Development Of Alzheimer’s Disease
- Are Hispanic Or Black
- Have An Immediate Family History Of A Person With Alzheimer’s Disease
- Experience Other Health Conditions Such As Heart Disease, High Blood Pressure, High Cholesterol, Diabetes, Or If You Have Had A Stroke.
- Gender And Alzheimer’s Disease:

- Women make up a Large Share of Alzheimer’s Patient than Men and Have a Greater Risk of Developing the Disease as They Age. Number of People Ages 65 And Older In The U.S. With Alzheimer’s. Percent Chance a Person Will Develop Alzheimer’s During Is His or Her Remaining Life Time.

Training:

- “Bringing Art to Life”
- Virtual reality program presenting two scenarios through continuum of AD
- Among a group of high school students working with seniors
• Improved empathy
• Increased enthusiasm
• Decreased stigma and negative attitudes
• Expanded awareness about what it is like to have Alzheimer's disease and dementia
• Ongoing project with medical and pharmacy students.

Treatment Of AD:

There is no cure for AD, and drug therapy for the disease is still in its infancy. Approved medications for the treatment of probable AD helps control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself. At present, the mainstay of AD therapy are drugs that target neurotransmitter systems in the brain. AD primarily damages glutamate and acetylcholine-producing neurons and their associated synapses, and this damage correlates well with early cognitive symptoms of AD. Acetylcholinesterase inhibitors help improve memory function and attention in AD patients by interfering with the breakdown of the neurotransmitter at the synapse. There are currently three FDA-approved cholinesterase inhibitors: rivastigmine and galantamine (for mild to moderate AD), and donepezil (for all stages of AD). Memantine is another FDA-approved medication for use in moderate to severe AD but belongs to a different class of drugs known as NMDA (glutamate) receptor antagonists. Both classes of medications are generally well-tolerated, with gastrointestinal upset, dizziness, and headache being the most common adverse effects observed. In recent years, a number of potential disease-modifying AD drugs have been evaluated in clinical trials, and several others are being evaluated in ongoing trials. Drugs that act to decrease the amount of Ab protein in the brain have received the most attention due to the prominent pathogenic role ascribed to Ab in the AD literature. One class of such drugs are secretase inhibitor. Which inhibit the secretase (protease) enzymes that cleave APP to produce Ab. Another strategy that has been attempted is by using drugs that promote the clearance of Ab through active or passive immunization. Regardless, other therapeutic strategies for AD are being investigated alongside the amyloid-based therapies, although with no major clinical successes yet to report. A promising avenue is the development of drugs that target the abnormal tau protein comprising the NFT. Another important source for potential AD drugs is the pool of medications on the market that are already approved for non-AD indications, such as diabetes, hypertension, and infectious disease. This strategy of drug ‘repurposing’ or ‘repositioning’ can greatly expedite the discovery of novel AD treatments and has been used in the past for other neurodegenerative disorders (e.g., anti-viral drug amantadine for use in Parkinson’s disease). An alternative explanation for the clinical trial failures is that the trials were conducted in patients with mild to moderate AD dementia, at a stage when the disease process is likely irreversible and brain damage is too great for the anti-AD therapy to have a clinically significant effect.
Mild Cognitive Impairment:
The MCI Concept:
MCI is a syndrome characterized by memory and/or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia. The most widely used clinical criteria for the diagnosis of MCI are those proposed by Petersen and colleagues at the Mayo Clinic. Researchers have also proposed several subtypes of MCI based on distinct neuropsychological profiles. Amnestic MCI involves memory-only impairments, while non-amnestic MCI involves only impairments in cognitive domains other than memory (e.g., executive function/attention, language, and visuospatial function). Multi-domain MCI is characterized by impairments in both memory and non-memory functions.

New Reports on Medications:
Antibodies (Ab)– Immunoglobulin (Ig):
• An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to neutralize pathogens
• The antibody recognizes a unique molecule of the pathogen, called an antigen
• Using this binding mechanism, an antibody can:
  • Tag a microbe or an infected cell for attack by other parts of the immune system (e.g., macrophages)
  • Or neutralize its target directly by impeding the biological process causing the disease by coating the pathogen, antibodies stimulate effector functions against the pathogen in cells.

Aducanumab: “Plaque Busters”:

Aducanumab Phase 1b:
Safety:
Higher doses associated with increased Amyloid Related Imaging Abnormality (ARIA)
Efficacy
Preliminary! Suggestion of better scores in treatment group than placebo group and
Improved amyloid imaging.

**Drug Studies Ongoing:**

- **Crenzumab:**
  - Binds to all types of amyloid (toxic fibrils and oligomers, but less to monomers)
  - Early studies disappointing, but larger Phase 3 study in early AD continues with higher dose

- **Gantenerumab:**
  - Human antibody binds to all forms of amyloid
  - Prodromal AD study stopped for no effect
  - Phase 3 early AD ongoing with higher dose.

**SURVEY OF THE FOLLOWING:**

The world’s population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer’s disease (AD), the most common cause of dementia. For comparison, according to the Centers for Disease Control and Prevention (2009-2012 estimates), about 3 million older adults in the United States have asthma, 10 million have diabetes, 20 million have arthritis, and 25 million have hypertension.

1. **Growth Of AD In The USA:**

Alzheimer’s disease is the sixth leading cause of death in the united states. 16.1 million Americans provide unpaid care for people with Alzheimer’s or other dementias. Here these caregivers provided an estimated 18.4 billion hours of care valued at over $232 billion. between 2000 and 2015 deaths from heart diseases have decreased 11% while deaths from Alzheimer’s disease have increased 123%. 1 in 3 seniors dies with Alzheimer’s or another dementias. It kills more than breast cancer and prostate cancer combined. No known way to stop, slow, or prevent this disease.

**Alzheimer’s Statistics-Michigan:**

Number of deaths from Alzheimer’s disease (2015) is 3,771; which is the sixth leading cause of death in michigan. 129% increase in Alzheimer’s death s since 2000. Caregivings (2017): 514,000 number of caregivers
.586,000,000 total hours of unpaid care.$7,395,000,000 total value of unpaid care.$363,000,000 highest health costs of caregivers.

**Medicaid:** $1.368 billion Medicaid costs of caring for people with Alzheimer’s (2018).

**Medicare:** $26,717 precipitate Medicare spending on people with dementia (2017).

2. **Epidemiology Of AD:**

An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec. In the United States, AD is the fifth leading cause of death among older adults, and about $200 billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).

3. **Advocacy And Fundraising- Impacting Research:**

5.7 Million Americans Are Living With Alzheimer’s .By 2050 This Number Is Projected To Rise To Nearly 14 Million. Every 65 Seconds Someone In The United States Develops The Disease..In 2018,Alzheimer’s And Other Dementias Will Cost The Nation $277 Billion. By 2050, These Costs Could Rise As High As$1.1 Trillion. Early And Accurate Diagnosis Could Save Upto $7.9 Trillion In Medical And Care Costs

This is achieved by funding Alzheimer’s research through the Alzheimer’s association leadership which includes following:

- $110 Million in 400+ current active studies located in 19 countries
- $440 Million total direct funding
- Over $5 Million total in MI
4. TREATMENT:

BAN2401 Clinical Trial Is Cautiously Optimistic:

- “Amyloid hypothesis:” lower levels of beta amyloid in the brain to slow or reverse Alzheimer’s in early AD
- 2017: No benefit at 12 months first look analysis
- 2018: Did slow disease course of 18 months which was planned completion based on several indicators
- First late-stage study successfully demonstrating potential disease-modifying effects in both clinical function and beta amyloid accumulation
- Support for beta amyloid as a target for AD therapy

MATERIALS AND METHODS:

1. CDC Reports That Alzheimer’s Cases Will Double By 2060:

A study conducted by the Centers for Disease Control and Prevention (CDC) is the first of its kind to forecast the effects of Alzheimer’s disease by ethnicity and race. The report found that the burden of Alzheimer’s and related forms of dementia will double by 2060, with minority populations having the largest increase due to population growth. In 2014, the burden of Alzheimer’s was five million people, accounting for 1.6% of the U.S. population. The CDC estimates that in 2060, Alzheimer’s cases will double, with the burden being 13.9 million people – almost 3.3% of the population. CDC Director, Robert R. Redfield, M.D., states, “This study shows that as the U.S. population increases, the number of people affected by Alzheimer’s and related dementias will rise, especially among minority populations. Early diagnosis is key to helping people and their families cope with loss of memory, navigate the health care system and plan for care in their future.” Because of population size, the CDC predicts that these populations will account for the largest increase in Alzheimer’s cases: African Americans (13.8%), Hispanic Americans (12.2%), Non-Hispanic Whites (10.3%), American Indian and Alaska Natives (9.1%), Asian and Pacific Islanders (8.4%)
2. Alzheimer’s will Be A Global Epidemic By 2050:

A new report titled, “Dementia: a public health priority” suggests that the number of people living with dementia will triple by 2050. The report was developed by the World Health Organization (WHO) and Alzheimer’s Disease International to raise awareness of dementia and advocate for action on an international level. The study uncovered startling statistics about the future of dementia and Alzheimer’s worldwide. Currently, there are 44 million people suffering from dementia globally. That number is up 22% over the past three years when there were 35.6 million people suffering from the disease. The report estimates that by 2050 over 135 million people worldwide will have dementia, tripling the amount of people who have it now.

3. Women’s Lifetime Risk for Developing Alzheimer’s Is Higher Than Men’s:

There are more than 5 million Americans living with Alzheimer’s and that number is expected to triple by 2050. A new report from the Alzheimer’s Association and the Shriver Report is giving us greater insight into the effects of the fatal disease and shows us just how burdensome it can be, especially on women.

Startling Statistics for Women And Alzheimer’s Disease:

A new report from the Alzheimer’s Association has found that women are at a higher risk for developing Alzheimer’s than men. Women are the epicenter of Alzheimer’s disease, representing a majority of both people with the disease and Alzheimer’s caregivers. Alzheimer’s Association Facts and Figures examines the impact of this unbalanced burden.”The numbers are shocking:

- Out of the 5 million people living with Alzheimer’s in the United States, 3.2 million are women.
- 1 out of 6 women over the age of 60 will develop Alzheimer’s, compared to 1 out of 11 men.
- Women in their 60s are twice as likely to develop Alzheimer’s than they are to develop breast cancer.
- The main reason that women are more likely to develop the neurological disease is simply that women live longer than men and that age is still the number one risk factor for developing Alzheimer’s. From that perspective, we are all at risk for Alzheimer’s.

Bearing The Burden Of Alzheimer’s:

Not only are women facing the brunt of the disease from a patient standpoint, women are also bearing the burden of caregiving. There are 2.5 times as many women than men providing 24 hour care for someone living with Alzheimer’s. 17% of female caregivers who feel isolated also feel depressed, compared to 2% of men. But, the burden is not just emotional. It is also financial:
20% of women exchanged their full time job for a part time job to act as a caregiver
18% of women took a leave of absence of work to provide caregiving
11% of women left work entirely
10% of women lost job benefits due to caregiving responsibilities

4. Meditation and Music May Alter Blood Markers Of Cellular Aging And Alzheimer’s Disease In Adults With Early Memory Loss:

Sixty older adults with subjective cognitive decline (SCD), a condition that may represent a preclinical stage of Alzheimer’s disease, participated in the randomized, clinical trial. While SCD has been linked to increased risk for dementia and associated with certain neuropathological changes implicated in Alzheimer’s disease development, including elevated brain levels of beta amyloid, this preclinical period may also provide a critical window for therapeutic intervention. In this trial, each participant was randomly assigned to either a beginner meditation (Kirtan Kriya) or music listening program and asked to practice 12 minutes/day for 12 weeks. At baseline and 3 months, blood samples were collected. Two markers of cellular aging were measured: telomere length and telomerase activity. (Telomeres serve as protective caps on chromosomes; telomerase is an enzyme responsible for maintaining telomere length). Blood levels of specific beta-amyloid peptides commonly linked to Alzheimer’s Disease were also assessed. In addition, memory and cognitive function, stress, sleep, mood, and quality of life were measured. All participants were followed for a total of 6 months. Following completion of the 3 month intervention period, the meditation group showed significantly greater increases in a key beta amyloid peptide (Aβ40) than did the music group. Rising beta amyloid levels were correlated with improvements in memory and cognitive function, as well as with those in mood, sleep, and quality of life at both 3 and 6 months; these positive associations were substantially more pronounced in the meditation group. Telomerase activity rose in both the meditation and music groups, although the increases were significant only among participants who had lower values at baseline (≤50th centile), and who practiced more frequently over the course of the intervention. Likewise, increases in telomere length were also significantly greater among participants with lower values at the beginning of the study. Increases in telomere length and telomerase activity were also correlated with improvements in certain cognitive and psychosocial outcomes.

CONCLUSION:

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options
available for managing AD. Alzheimer’s disease Neuroimaging Initiative (ADNI) beginning in 2004. The ADNI, which is a kin to the Framingham Heart Study in its ambitions, is a public private partnership and the largest project of its kind that seeks to collect longitudinal neuroimaging data along with clinical data, neuropsychological assessments, and biological specimens (e.g., blood and CSF) from MCI, AD, and healthy older subjects. The ADNI and similar large-scale initiatives are likely to rapidly advance our knowledge on dementia and AD and will catalyze the development of significantly more effective therapies for AD than exist today.

1. moderate-to-high intensity exercise in patients with mild AD. Exercise reduced neuropsychiatric symptoms in patients with mild AD, with possible additional benefits of preserved cognition in a subgroup of patients exercising with high attendance and intensity

2. Both groups of meditation and music improved significantly in memory and cognitive function, as well as in sleep and psychological status, although improvements in stress, mood, and quality of life were substantially, greater in the meditation group three months after the intervention ended. These improvements were maintained or further strengthened at six months

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