CHAPTER 3

ALZHEIMER’S DISEASE AND IT’S TREATMENT

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Alzheimer's disease (AD), also known as Senile Dementia of the Alzheimer Type (SDAT) or simply Alzheimer’s is the most common form of dementia. This incurable, degenerative, terminal disease was first described by a German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him.

Alzheimer's disease (AD) is a slowly progressive disease of the brain that is characterized by impairment of memory and eventually by disturbances in reasoning, planning, language, and perception.

Many scientists believe that Alzheimer's disease results from an increase in the production or accumulation of a specific protein (beta-amyloid protein) in the brain that leads to nerve cell death.
Generally, it is diagnosed in people over 65 years of age, although the less-prevalent early onset of Alzheimer’s can occur much earlier.

In 2006, there were 26.6 million sufferers worldwide.

Alzheimer’s is predicted to affect 1 in 85 people globally by 2050.
Stages of Alzheimer’s Disease

As Alzheimer’s disease progresses, neurofibrillary tangles spread throughout the brain (shown in blue). Plaques also spread throughout the brain, starting in the neocortex. By the final stage, damage is widespread and brain tissue has shrunk significantly.
Symptoms of Developing A.D

1) Early Stage
- This is considered as a mild/early stage and the duration period is 2-4 years.
- Frequent recent memory loss, particularly of recent conversations and events.
- Repeated questions, some problems expressing and understanding language.
- Writing and using objects become difficult and depression and apathy can occur.
- Drastic personality changes may accompany functional decline.
- Need reminders for daily activities and difficulties with sequencing impact driving early in this stage.
2) **Second stage**
- This is considered as a middle/moderate stage and the duration is 2-10 years.
- Can no longer cover up problems.
- Pervasive and persistent memory loss impacts life across settings.
- Rambling speech, unusual reasoning, confusion about current events, time, and place.
- Potential to become lost in familiar settings, sleep disturbances, and mood or behavioral symptoms accelerate.
- Nearly 80% of patients exhibit emotional and behavioral problems which are aggravated by stress and change.
- Slowness, rigidity, tremors, and gait problems impact mobility and coordination.
- Need structure, reminders, and assistance with activities of daily living.
3) **Moderate stage**

- Increased memory loss and confusion.
- Problems recognizing family and friends.
- Inability to learn new things.
- Difficulty carrying out tasks that involve multiple steps (such as getting dressed).
- Problems coping with new situations.
- Delusions and paranoia.
- Impulsive behavior.
- In moderate AD, damage occurs in areas of the brain that control language, reasoning, sensory processing, and conscious thought.
4) Last stage

- This is considered as the severe stage and the duration is 1-3 years.
- Confused about past and present. Loss of recognition of familiar people and places
- Generally incapacitated with severe to total loss of verbal skills.
- Unable to care for self. Falls possible and immobility likely.
- Problems with swallowing, incontinence, and illness.
- Extreme problems with mood, behavioral problems, hallucinations, and delirium.
- Patients need total support and care, and often die from infections or pneumonia
Diagnosis of Alzheimer’s Disease

- Alzheimer’s disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions.

- Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computer tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.

- The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically.
PET scan of the brain of a person with AD showing a loss of function in the temporal lobe.
Neuropsychological tests such as the mini-mental state examination (MMSE) are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease.

Psychological tests for depression are employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause.

When available as a diagnostic tool, SPECT and PET neuroimaging are used to confirm a diagnosis of Alzheimer’s in conjunction with evaluations involving mental status examination. In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer’s disease from other possible causes, compared with the usual attempts employing mental testing and medical history analysis.
Scientists don’t yet fully understand what causes AD, but it is clear that it develops because of a complex series of events that take place in the brain over a long period of time. It is likely that the causes include genetic, environmental, and lifestyle factors.

- Some drug therapies propose that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.
- Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid leading to generalized neuroinflammation.
- Alzheimer’s disease is characterized by a build-up of proteins in the brain. Though this cannot be measured in a living person, extensive autopsy studies have revealed this phenomenon. The build-up manifests in two ways:
  - **Plaques** - deposits of the protein *beta-amyloid* that accumulate in the spaces between nerve cells
  - **Tangles** - deposits of the protein *tau* that accumulate inside of nerve cells
Microscopy image of a neurofibrillary tangle, conformed by hyperphosphorylated tau protein.
Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD.

Plaques are dense, mostly insoluble deposits of amyloid - beta peptides and cellular material outside and around neurons.

Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves.

Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of AD patients have a greater number of them in specific brain regions such as the temporal lobe.
Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain. Plaques are made up of small peptides, 39-43 amino acids in length, called beta-amyloid (also written as A-beta or Aβ).

Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane.

APP is critical to neuron growth, survival and post-injury repair. In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis.

One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules.

These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called tau stabilizes the microtubules when phosphorylated, and is therefore called a microtubule-associated protein.

In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.
Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.
Exactly how disturbances of production and aggregation of the beta amyloid peptide gives rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that AB selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilization of glucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response.

Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain derived neurotrophic factor (BDNF) have been described in AD.
Apolipoprotein E (APOE) found on chromosome 19 appears to be a predisposing genetic risk factor for the late onset of AD - the most typical AD.

- APOE helps carry cholesterol in the bloodstream.
- APOE comes in several different forms, or alleles.
- Three forms—APOE ε2, APOE ε3, and APOE ε4—occur most frequently.
Medicines used to treat A.D and its Symptoms

- **Aricept**
  Donepezil
  Used to delay or slow the symptoms of AD
  - Loses its effect over time
  - Used for mild, moderate and severe AD
  - Does not prevent or cure AD

- **Celexa**
  Citalopram
  Used to reduce depression and anxiety
  - May take 4 to 6 weeks to work
  - Sometimes used to help people get to sleep

- **Depakote**
  Sodium Valproate
  Used to treat severe aggression
  - Also used to treat depression and anxiety

- **Exelon**
  Rivastigmine
  Used to delay or slow the symptoms of AD
  - Loses its effect over time
  - Used for mild to moderate AD
  - Can get in pill form or as a skin patch
  - Does not prevent or cure AD
- **Namenda**
  - Memantine
  - Used to delay or slow the symptoms of AD
  - Loses its effect over time
  - Used for moderate to severe AD
  - Sometimes given with Aricept®, Exelon®
  - Does not prevent or cure AD

- **Razadyne**
  - Galantamine
  - Used to prevent or slow the symptoms of AD
  - Loses its effect over time
  - Used for mild to moderate AD
  - Can get in pill form or as a skin patch
  - Does not prevent or cure AD

- **Zoloft**
  - Sertraline
  - Used to reduce depression and anxiety
  - May take 4 to 6 weeks to work
  - Sometimes used to help people get to sleep

- **Trileptal**
  - Oxcarbazepine
  - Used to treat severe aggression
  - Also used to treat depression and anxiety

- **Tegretol**
  - Carbamazepine
  - Used to treat severe aggression
  - Also used to treat depression and anxiety

- **Remeron**
  - Mirtazapine
  - Used to reduce depression and anxiety
  - May take 4 to 6 weeks to work
  - Sometimes used to help people get to sleep
Although there is currently no way to cure Alzheimer's disease or stop its progression, researchers are making encouraging advances in Alzheimer's treatment, including medications and non-drug approaches to improve symptom management.

Mild/Moderate AD:

Cholinesterase inhibitors increase the levels of acetylcholine in the brain, which plays a key role in memory and learning. This kind of drug postpones the worsening of symptoms for 6 to 12 months in about half of the people who take it. Cholinesterase inhibitors most commonly prescribed for mild to moderate Alzheimer's disease include Aricept (donezepil HCL), Exelon (rivastigmine), and Razadyne (galantamine).
Moderate/Severe AD:

**Namenda** (memantine) regulates glutamate in the brain, which plays a key role in processing information. This drug is used to treat moderate to severe Alzheimer's disease and may delay the worsening of symptoms in some people. It may allow patients to maintain certain daily functions a little longer than they would without the medication.
Razadyne

- Razadyne (galantamine HBr) is FDA-approved for mild and moderate stages of the disease.
- Razadyne is a cholinesterase inhibitor that prevents the breakdown of acetylcholine in the brain. Acetylcholine plays a key role in memory and learning; higher levels in the brain help nerve cells communicate more efficiently. Razadyne also stimulates nicotinic receptors to release more acetylcholine in the brain.
Razadyne delays the worsening of Alzheimer's symptoms for 6 to 12 months in about half of the people who take it.

Razadyne is available in tablet and capsule form, and is commonly started at 4 mg twice a day. If it's well tolerated after 4 weeks, the dosage may be increased to 8 mg twice a day.

Razadyne also comes in an extended release, once-a-day tablet.

Razadyne is available in generic form (galantamine HBr).
Exelon (Rivastigmine)

- Exelon is FDA approved for mild and moderate stages of the disease; it is also approved for the treatment of mild to moderate dementia due to Parkinson's disease.
- Exelon is available as a capsule, liquid, and patch.
Exelon is a cholinesterase inhibitor that prevents the breakdown of acetylcholine and butyrylcholine in the brain by blocking the activity of two different enzymes. Acetylcholine and butyrylcholine play a key role in memory and learning.

When given orally, bioavailability is about 40% in the 3 mg dose. The compound can cross the blood-brain barrier.
Aricept (Donepezil)

- One of the most widely used drugs to treat the symptoms of Alzheimer's disease. Aricept is FDA-approved for mild, moderate, and severe stages of the disease.
Aricept is available in tablet form or an orally disintegrating tablet form, and is commonly started at 5 mg a day.

Can cross the blood-brain barrier.
Namenda (Memantine)

- Namenda is an N-methyl D-aspartate (NMDA) antagonist that regulates the activity of glutamate in the brain. Glutamate plays a key role in memory and learning, but excess glutamate can lead to the disruption of nerve cell communication or nerve cell death.
References

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