Alzheimers Disease: Comprehensive Overview

1 Definition

Alzheimers disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired daily functioning. It is the most common cause of dementia, primarily affecting older adults, and is marked by the accumulation of amyloid-beta plaques and tau neurofibrillary tangles in the brain.

2 Etiopathogenesis

Alzheimers disease results from a complex interplay of genetic, environmental, and biological factors:

- **Genetic Factors**:
  - Early-onset AD (<65 years): Mutations in APP, PSEN1, and PSEN2 genes.
  - Late-onset AD (>65 years): APOE 4 allele increases risk.
- **Environmental Factors**: Head trauma, vascular risk factors (e.g., hypertension, diabetes), and low education level.
- **Biological Mechanisms**:
  - Amyloid-beta (A) accumulation due to impaired clearance or overproduction.
  - Tau protein hyperphosphorylation forming neurofibrillary tangles.
  - Neuroinflammation and oxidative stress.
  - Synaptic and neuronal loss.
- **Risk Factors**: Aging (primary risk factor), female gender, family history, and cardiovascular disease.

3 Clinical Manifestations

AD progresses through stages with worsening cognitive and functional impairment:

- **Early Stage**: Mild memory loss (e.g., forgetting recent events), difficulty with problem-solving, and mild language issues.

- **Middle Stage**: Increased memory loss, disorientation, difficulty recognizing family, and impaired activities of daily living (ADLs).
- **Late Stage**: Severe cognitive decline, loss of communication, immobility, and susceptibility to infections (e.g., pneumonia).
- **Associated Features**: Behavioral changes (agitation, aggression), mood disorders (depression, apathy), and psychosis (hallucinations, delusions).
- **Complications**: Aspiration pneumonia, falls, and malnutrition.

4 Pathophysiology

AD involves amyloid and tau pathology leading to neuronal dysfunction and cognitive decline. The flowchart below illustrates the key mechanisms.

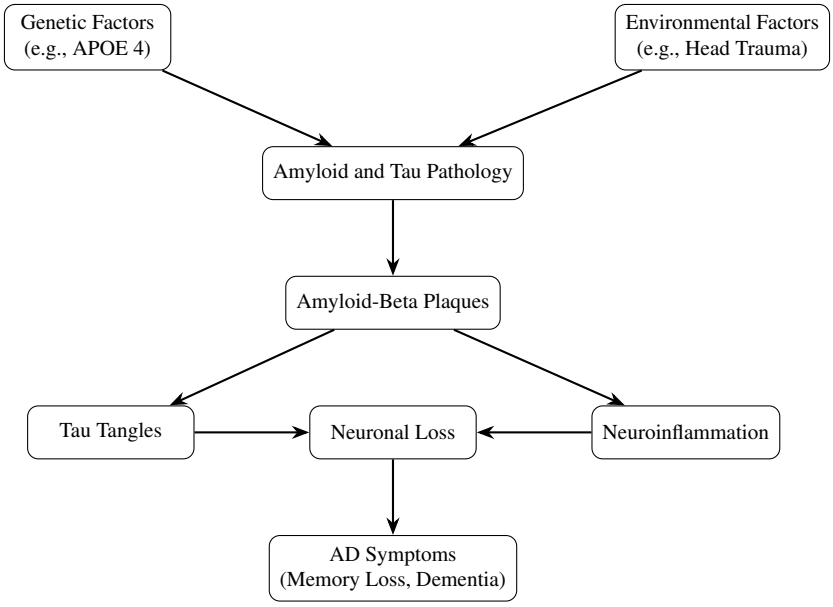

Figure 1: Pathophysiology of Alzheimers Disease

5 Symptoms

- **Cognitive Symptoms**:
  - Memory loss (especially recent memory).
  - Difficulty with language (e.g., word-finding issues).
  - Impaired executive function (e.g., planning, decision-making).
  - Visuospatial deficits (e.g., getting lost).
- **Behavioral/Psychiatric Symptoms**:
  - Depression, apathy, or anxiety.
  - Agitation, aggression, or wandering.

  - Hallucinations or delusions (later stages).
- **Functional Symptoms**: Difficulty with ADLs (e.g., dressing, eating) progressing to dependency.
- **Late-Stage Symptoms**: Loss of speech, immobility, and swallowing difficulties.

6 Diagnosis

Diagnosis is based on clinical criteria, supported by biomarkers and imaging:

- **Clinical Criteria (NIA-AA)**: Progressive cognitive decline, memory impairment, and exclusion of other causes.
- **Cognitive Testing**: Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) to assess severity.
- **Neuroimaging**:
  - MRI: Assess cortical atrophy (e.g., hippocampal volume loss).
  - PET: Amyloid or tau imaging to confirm pathology.
- **Biomarkers**: Cerebrospinal fluid (CSF) analysis for low A42, high tau, or high phospho-tau.
- **Laboratory Tests**: Rule out reversible causes (e.g., vitamin B12 deficiency, hypothyroidism).
- **Differential Diagnosis**: Exclude vascular dementia, Lewy body dementia, or frontotemporal dementia.

7 Nonpharmacological Management

Nonpharmacological strategies focus on improving quality of life and function:

- **Cognitive Stimulation**: Engage in memory exercises, puzzles, or cognitive training programs.
- **Physical Activity**: 150 minutes/week of moderate exercise (e.g., walking) to maintain mobility and reduce depression.
- **Diet**: Mediterranean or DASH diet to support brain health and reduce cardiovascular risk.
- **Social Engagement**: Support groups or social activities to reduce isolation.
- **Caregiver Support**: Education and respite care to manage caregiver burden.
- **Safety Measures**: Home modifications (e.g., removing trip hazards), wander prevention (e.g., ID bracelets).
- **Behavioral Management**: Non-drug approaches for agitation (e.g., music therapy, structured routines).

8 Pharmacological Management

Medications aim to manage symptoms, as no disease-modifying treatments are widely available:

- **Cognitive Enhancers**:
  - **Cholinesterase Inhibitors**: Donepezil (5–10 mg/day), rivastigmine (3–12 mg/day), or galantamine (8–24 mg/day) for mild-to-moderate AD.
  - **NMDA Receptor Antagonist**: Memantine (5–20 mg/day) for moderate-to-severe AD.
- **Symptomatic Treatment**:
  - SSRIs (e.g., sertraline 50–200 mg/day) for depression.
  - Antipsychotics (e.g., quetiapine 25–200 mg/day) for severe agitation or psychosis (use cautiously due to risks).
  - Benzodiazepines (e.g., lorazepam 0.5–2 mg as needed) for acute agitation, short-term only.
- **Emerging Therapies**: Anti-amyloid antibodies (e.g., aducanumab, lecanemab) for early AD, though limited by availability and side effects.
- **Comorbidity Management**: Treat hypertension, diabetes, or dyslipidemia to reduce vascular contributions.
- **Monitoring**: Regular assessment of cognitive function, side effects, and caregiver feedback.