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EARLY – ONSET ALZHEIMER'S, CAUSES, SYMPTOMS, AND MANAGEMENT

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ABSTRACT

Early – Onset Alzheimer's Disease (EOAD) is a rare but serios neurodegenerative disorder that affects individuals typically below 65 years of age unlike late – onset Alzheimer's EOAD often progresses more rapidly and has a stronger genetic component it is characterized by progressive cognitive decline , memory impairment, behavioral changes and loss of functional independence the pathophysiology involves accumulation of amyloid-beta plaques tau protein tangles neuroinflammation and neuronal loss Early diagnosis is challenging due to atypical presentation and misdiagnosis as psychiatric disorders- modifying therapies such as monoclonal antibodies have improved early detection and management this review discusses

the causes clinical manifestations pathophysiology diagnosis and current management strategies of EOAD along with recent therapeutic advancements from 2020-2025.

KEYWORDS: Early -onset Alzheimer's, Amyloid-beta, Tau Protein, Neurodegeneration, Dementia, Biomarkers, Monoclonal Antibodies, Cognitive Decline.

1.0 INTRODUCTION

Alzheimer's disease is a progressive brain disorder that leads to memory loss and cognitive impairment while most cases occur after 65 years (late -onset) Early – onset Alzheimer's (EOAD) occurs between 30-65 years of age and progresses more aggressively. the disease is characterized by the degeneration of neurons, especially in the hippocampus and cerebral cortex, leading to memory loss, impaired thinking, behavioral changes.

2.0 Causes and Risk Factors

2.1 Genetic Causes

EOAD is predominantly associated with autosomal dominant genetic mutations making it distinct from late -onset forms the three principal genes involved are

Amyloid Precursor Protein (APP)

Mutations in the APP gene lead to abnormal cleavage of the protein, resulting in excessive production of amyloid -beta (Aβ42) which is highly prone to aggregation

Presenilin 1 (PSEN1)

The most common cause of familial EOAD.PSEN1 mutations alter γ-secretase activity, increasing disease onset, sometimes as early as the 30s

Presenilin 2 (PSEN2)

Less common but similar in mechanism to PSEN1. it shows variable penetrance and slightly later onset these mutations promote early accumulation of amyloid plaques, triggering downstream neurovegetative processes

2.2 Non – Genetic Risk Factors

Although genetics is central several modifiable and non – modifiable factors influence disease onset and progression

Family history (even without identified mutations)

Traumatic brain injury (TBI) leading to chronic neuroinflammation

Cardiovascular disorders such as hypertension, diabetes, and atherosclerosis impair cerebral perfusion

Metabolic syndrome and insulin resistance (linked with Type 3 diabetes hypothesis)

Lifestyle factors

Sedentary behaviour

High-fat, low – nutrient diet

Smoking and alcohol use

Oxidative stress which damages neuronal membranes and mitochondria

2.3 Environmental Factors

Environmental exposures can accelerate neurodegeneration

Heavy metals (lead, mercury)

Air pollution (PM2.5 exposure linked to neuroinflammation)

Chronic psychological stress (elevated cortisol damaging hippocampus)

Poor sleep quality affecting amyloid clearance via glymphatic system

3.0 Pathophysiology of EOAD

EOAD involves a multifactorial cascade of neurodegenerative mechanisms

3.1 Amyloid Plaque Formation

Amyloid – beta peptides aggregate extracellularly to form plaques these plaques

Disrupt synaptic Communication

Induce oxidative stress

Active inflammatory responses

3.2 Tau Protein Tangles

Tau proteins stabilize microtubules in EOAD

Tau becomes hyperphosphorylated

Forms neurofibrillary tangles (NFTs)

Leads to cytoskeletal collapse and neuronal death

3.3 Neuroinflammation

Microglia become chronically activated

Release cytokines (IL-1β, TNF-α)

Sustained inflammation Worsens neuronal injury

3.4 Synaptic Dysfunction and Neuronal loss

Loss of synaptic plasticity

Impaired neurotransmitter release (especially acetylcholine)

Progressive neuronal apoptosis

3.5 Brain Atrophy

Significant shrinkage of Hippocampus (memory center)

Cortical thinning in frontal and temporal lobes

Correlates with disease severity

4.0 Clinical Symptoms

4.1 Cognitive symptoms

Early episodic memory loss

Difficulty in executive functioning (planning, Organizing)

Impaired attention and concentration

Language deficits (word -finding difficulty, aphasia)

4.2 Behavioural and Psychiatric Symptoms

Depression (common early sign)

Anxiety and emotional instability

Aggression, irritability

Personality Changes

Psychosis in advanced stages

4.3 Functional Impairment

Difficulty managing finances, medications

Reduced work performance

Dependence in activities of daily living (ADLs)

4.4 Atypical Presentation in EOAD

Unlike late – onset cases

Prominent visual-spatial deficits

Apraxia (difficulty performing learned movements)

Early executive dysfunction

Faster progression

5.0 Diagnosis of EOAD

5.1 Clinical Assessment

Detailed patient and family history

Cognitive scales MMSE (Mini-Mental State Examination) MoCA (Montreal cognitive Assessment)

Functional and behavioural evaluation

5.2 Biomarkers

Modern diagnostics rely on biomarkers, CSF biomarkers, ↓ Amyloid-beta,

↑ Total tau and phosphorylated tau, Blood based biomarkers (emerging), Plasma p-tau 181, Neurofilament light chain (NfL), These allow early and less invasive detection

5.3 Neuroimaging

MRI – Detects brain atrophy patterns

PET scan

Amyloid PET -plaque detection

Tau PET- tangle visualization

5.4 Genetic Testing

Early onset (<60 years)

Strong family history

Helps confirm diagnosis and guide counselling

6.0 Management of EOAD

6.1 Pharmacological Treatment

6.1.1 Symptomatic Therapy

Cholinesterase inhibitors (donepezil, Rivastigmine. Galantamine)

Increase acetylcholine levels

Improve cognition temporarily

Memantine

NMDA receptor antagonist

Reduces glutamate toxicity

6.1.2 Disease – Modifying Therapies

Lecanemab, Targets soluble amyloid aggregates, Slows cognitive decline, Donanemab

Clears amyloid plaques, Shows promising clinical trial outcomes, Limitations

Risk of ARIA (Amyloid- Related Imaging Abnormalities), High cost and monitoring requirements

6.2 Non -Pharmacological Management

Cognitive stimulation therapy

Occupational therapy

Behavioural therapy

Support groups and counselling

6.3 Lifestyle Modifications

Regular aerobic exercise (improves neuroplasticity)

Mediterranean diet (rich in antioxidants, omega -3)

Sleep hygiene (enhances amyloid clearance)

Stress reduction (Yoga, meditation)

7.0 Emerging Therapies and Research

7.1 Anti – Amyloid Strategies

Monoclonal antibodies

BACE inhibitors (limited success due to side effects

7.2 Tau-Targeting Therapies

Tau aggregation inhibitors

Kinase inhibitors (e.g. GSK-3 inhibitors)

7.3 Gene Therapy

CRISPR- based correction of mutations

Still in experimental stages

7.4 Stem Cell Therapy

Potential neuronal regeneration

Challenges – integration, safety, ethical concerns

7.5 AI Based Drug Discovery

Accelerates identification of drug targets

Enables personalized medicine

Predicts disease progression

8.0 Complications of EOAD

Severe cognitive impairment

Total dependency on caregivers

Increased susceptibility to infections (pneumonia common cause of death)

Malnutrition and dehydration

Psychological burden (both patient and caregivers)

Economic burden due to long -term care

9.0 Prognosis

EOAD typically shows, Faster progression than late – onset Alzheimer's, Average survival 8-15 years, post – diagnosis, Factors affecting prognosis, Genetic mutations (PSEN1- more aggressive), Early diagnosis and intervention, Support Systems and care quality, Despite no cure, early intervention improves, Functional independence, Quality of Life, Disease management outcomes

10.0 CONCLUSION

Early -onset Alzheimer's disease represents a clinically and genetically distinct represents a clinically and genetically distinct form of dementia with profound personal, social, and economic consequences its early onset during productive years makes it particularly devastating for patients and families Advances in biomarker research, neuroimaging and disease-modifying therapies have significantly improved early detection and management the introduction of monoclonal antibodies marks a shift toward targeted therapy although challenges such as cost accessibility and safety remain Future directions including gene therapy stem cell approaches, and AI driven drug discovery offer promising avenues for more effective and personalized treatments however a multidisciplinary approach combining pharmacological treatment lifestyle interventions and psychosocial support remains essential for optimal patient care

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