Early Onset Dementia: Assessment, Burden & Challenges

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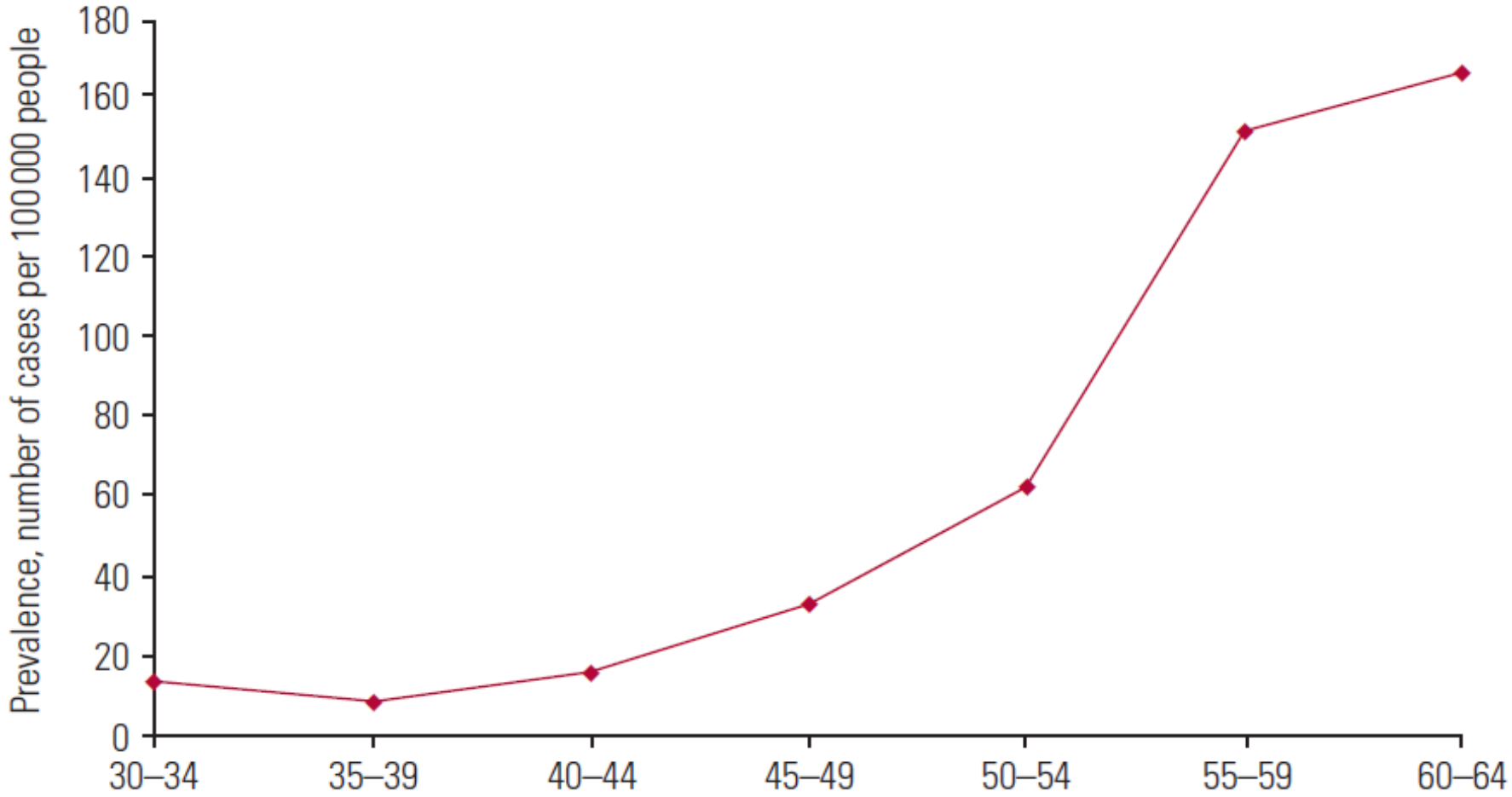
Introduction

- Dementia is among the greatest global health crises of the 21st century.
- Early-onset dementia is conventionally thought to include patients with **onset before 65 years** of age.
- A consequence of the first challenge is a delay in a specific diagnosis of the cause of the dementia.

Prevalence of Dementia By Age



Younger-Onset AD

- Of the people who have AD, about **5% develop symptoms before 65**.
- Most people with early-onset Alzheimer's develop symptoms of the disease in their 40s and 50s.
- Some people with early-onset Alzheimer's have the most common form of the disease.

https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048356

Familial Alzheimer's Disease

- They're likely to have a parent or grandparent who also developed Alzheimer's at a younger age.
- Early-onset Alzheimer's that runs in families is linked to three genes — the APP, PSEN 1 and PSEN 2, different from the APOE gene that increases your risk for AD.

https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048356

Standard Criteria for Dementia

- Standard criteria for dementia require that
  1. **Cognitive** impairment is sufficiently severe to compromise social and occupational functioning
  2. **Memory** must be specifically impaired

Standard Criteria for Dementia: Cont.

- EOD is a frequently misdiagnosed condition, with 30–50% of cases reported as mistaken or uncertain diagnoses
    1. The diagnoses of EOD are more diverse than the diagnoses of LOD
    2. EOD may present **salient cognitive deficits** apart from loss of memory and convulsive paraparesis, spasms or myoclonus
- EOD frequently appears together with **neuropsychiatric characteristics** that are out of proportion to cognitive deficits

ASSESSMENT

Step 1: Detect the Role of Primary Care in the Early Detection

- The insidious and variable emergence of symptoms associated with AD and other dementias can make recognition extremely challenging, particularly in a primary care setting.

CHARACTERISTICS OF EARLY-ONSET ALZHEIMER'S DISEASE
COMPARED TO LATE-ONSET ALZHEIMER'S DISEASE

1. **Larger percentage of non-amnestic phenotypic variants** (logopenic variant primary progressive aphasia, posterior cortical atrophy, behavioural/ dysexecutive syndrome, acalculia, corticobasal syndrome)

2. **More aggressive course with high rate of mortality**

3. **Greater delay in diagnosis**

4. **More likely to have genetic predisposition:** 1 in 10 may harbour autosomal dominant familial AD genetic mutation

5. **Neuroimaging findings:**
   - Less hippocampal and mesial temporal lobe atrophy
   - Greater posterior (parietal, temporoparietal junction) cortical atrophy

6. **Greater psychosocial problems** (unexpected midlife 'out-of-step' loss; continued work, financial, family responsibilities; retained insight with depression, anxiety and suicide risk)

Step 2: Assess and Differentiate
Example questions for a clinician conducting an initial assessment with a patient and caregiver

Required information	Example questions for the patient and/or informant
Medical history	Has the patient had any recent illnesses? Has the patient recently had any head injuries? Has the patient used any medications recently that could cause memory loss? Has the patient used or been exposed to any illicit drugs? Is there a history of epilepsy?
Risk factors	Is there a history of dementia within the family?
	Does the patient have any other medical conditions, such as cardiovascular disease or obesity?
	Is the patient a smoker or ex-smoker?
Cognitive and behavioral changes	What does a typical day look like for you (the patient)? Has the patient noticed they are forgetting things or misplacing items recently? Has the patient noticed any changes to their mood or felt helpless recently? Has the patient had any issues with finances?
Physical	Has the patient had any falls recently? Has the patient noticed any issues with their balance?
Other	Does the patient have any vision or hearing problems? Is there anything else the patient or caregiver is concerned about?

Clinical Features of Delirium Versus Dementia

Feature	Delirium	Dementia
Progression	Fluctuating with lucid intervals, often worse at night	Fairly consistent over the course of a day
Consciousness	Altered	Clear
Attention	Impaired with pronounced distractibility	Relatively normal
Memory	Impaired	Impaired
Thinking	Disorganised, delusional	Paucity of thought
Sleep–wake cycle	Disrupted	Often normal
Perception	Hallucinations and illusions common, often visual	Hallucinations generally absent in early stages

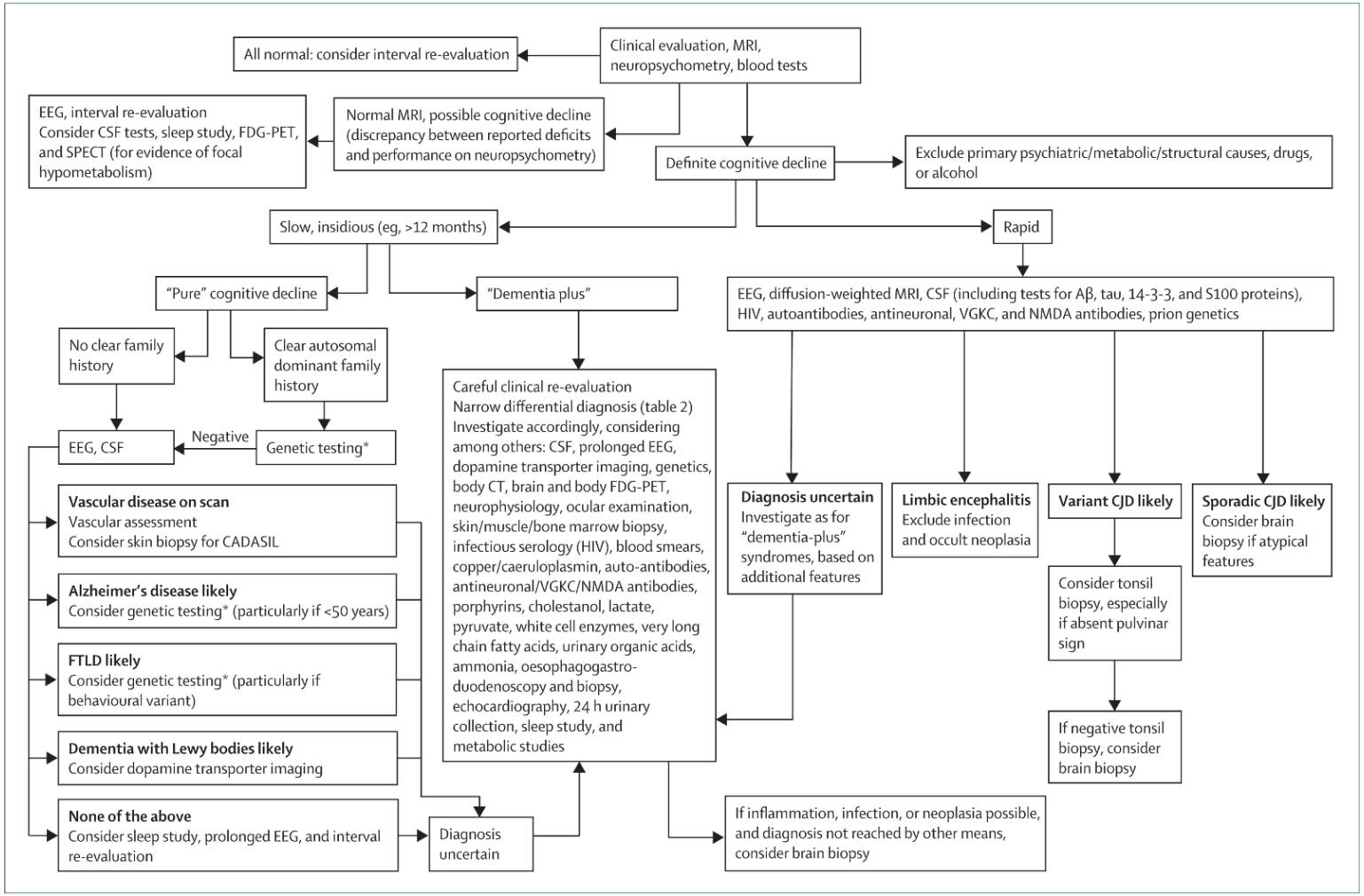
Comparison of Cortical and Subcortical Dementia according to Neuropsychological profile

Characteristic	Cortical	Subcortical
Speed of cognitive processing	Normal	Slowed
Planning, problem solving, initiative (frontal "executive" abilities)	Preserved in early stages	Impaired from onset
Personality	Intact until late, unless frontal type	Apathetic, withdrawn
Memory	Severely amnesic	Forgetful
Language	Aphasia	Normal except for dysarthria and reduced output
Visuospatial and perceptual difficulties	Impaired	Impaired
Mood	Depression not uncommon in early Alzheimer's disease	Depression common
Agnosia/prosopagnosia	Often present	Not usually seen

Abnormal Neurological Signs and Their Significance in Dementia

Physical sign	Seen in
Ataxia	Paraneoplastic disease, cerebellar tumour, Whipple's disease, Creutzfeldt-Jakob disease (CJD), AIDS dementia complex, spinocerebellar ataxia (SCA), Wernicke-Korsakoff syndrome, Hallervorden-Spatz, ornithine transcarbamylase deficiency, Niemann-Pick disease, mitochondrial disorders, adrenoleucodystrophy, neurodegeneration with brain iron accumulation (NBIA), lead poisoning
Involuntary movements	Huntington's disease (HD), inherited metabolic disorders including Wilson's disease, CJD, corticobasal degeneration (CBD), systemic lupus erythematosis, Whipple's disease, Hallervorden Spatz, Lesch-Nyhan
Myoclonus	Post-anoxia, CJD, Alzheimer's disease (AD), subacute sclerosing panencephalitis (SSPE), myoclonic epilepsies, Hashimoto's encephalopathy, dementia with Lewy bodies, CBD
Extrapyramidal signs	Dementia with Lewy bodies, Parkinson's disease, progressive supranuclear palsy (PSP), vascular dementia, frontotemporal dementia (FTD), CJD, Wilson's disease, HD, dentato-rubro-pallido-luysian atrophy (DRPLA), neuroacanthocytosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), Niemann-Pick, mitochondrial disorders, NBIA
Pyramidal signs	Motor neuron disease, CJD, LCBD, B12 deficiency, multiple sclerosis (MS), SCA, multi system atrophy, hydrocephalus, AD, Hallervorden Spatz, CADASIL, mitochondrial disorders, adrenoleucodystrophy, FTD
Optic disc pallor	MS, B12 deficiency
Papilloedema	Tumour, subdural haematoma, hydrocephalus
Cortical blindness	Vascular disease, AD, CJD
Anosmia	Subfrontal meningioma, head injury, AD, PD, HD
Abnormal eye movements	Progressive supranuclear palsy, Wernicke-Korsakoff, Whipple's disease, CBD, mitochondrial cytopathies, cerebellar tumours, causes of raised intracranial pressure, CJD, mitochondrial disorders, HD, Niemann Pick type C
Other cranial nerve signs	Sarcoidosis, tumours, neoplasia, tuberculous meningitis
Alien hand	CBD
Visual field defect	Tumour, vascular disease, CJD
Pupillary abnormalities (Argyll Robertson pupil)	Neurosyphilis
Peripheral neuropathy	Vitamin B12 deficiency, paraneoplastic disorders, neuroacanthocytosis, spinocerebellar ataxia, Hallervorden Spatz, adrenoleucodystrophy, NBIA, lead poisoning, systemic lupus erythematosus (SLE)
Early onset incontinence	Tumour, hydrocephalus, PSP
Bulbar features	Frontal dementia (motor neuron disease)
Fasciculations	Frontal dementia (motor neuron disease), rarely CJD
Seizures	Vasculitis, neoplasia, primary angiitis of the nervous system, limbic encephalitis, AIDS dementia complex, neurosyphilis, SSPE, Hashimoto's encephalopathy
Grimacing facial expression	Wilson's disease

Flow chart for Assessment and Investigation of Young-Onset Dementia



Step 3: Diagnose

	AD	VaD	LBD	FTD
History	Gradual onset and progression	Abrupt or gradual onset Stepwise or gradual progression	Insidious onset Progression with fluctuations	Early onset, insidious onset Rapid progression
Examination	Normal gait, normal neurological exam in early to mild stages	Gait abnormalities, signs of vascular disease and focal neurological signs	Shuffled gait, increased tone, tremors, slow moving	At late stage, patients develop gait abnormalities along with primitive reflexes
Others signs and symptoms	Memory loss, language deficits, mood swings and personality changes	Memory loss, language deficits, dysarthria, emotional lability, decreased concentration	Depression, hallucinations, variable in terms of day to day symptoms	Poor judgement, social withdrawal and social inappropriate behaviour
Imaging	Generalized atrophy with noted medial temporal atrophy	Strokes, lacunar infarcts, white matter lesions	Generalized atrophy	Frontal and temporal lobes atrophy
Pathology	Beta amyloid plaques and neurofibrillary tangles	Cerebrovascular disease due to vascular risk factors	Lewy bodies in both cortex and midbrain areas	Absence of plaques and tangles. Pick cells and bodies in cortex

Diagnosis of EOD

- An important part of assessing patients with early-onset AD is determining their **family history and the need for genetic testing and genetic counseling.**
- One major difference between early-onset and late-onset Alzheimer disease is that one-third or more of patients with early-onset Alzheimer disease present with **language, visuospatial, or other phenotypes rather than the usual amnestic disorder** seen in late-onset Alzheimer disease.
- CSF analysis in early-onset Alzheimer disease is similar to late-onset Alzheimer disease, showing the characteristic low amyloid-β1-42 and high total tau and phosphorylated tau levels but with some variations.

Step 4: Treatment

- The management of early-onset AD may differ from late-onset AD when targeting the management of specific cognitive and behavioral deficits.
- Patients with behavioral/dysexecutive AD may require use of psychoactive medications to manage egregious behaviors, when present.

Treatment: Cont.

Pharmacological interventions

- Anti-dementia drugs for patients of any age are donepezil, rivastigmine, galantamine and memantine. The available evidence base confirms that the acetylcholinesterase inhibitors are effective across the spectrum of Alzheimer's disease (mild, moderate and severe disease) and they also lead to improvements in non-cognitive symptoms.

Treatment: Cont.

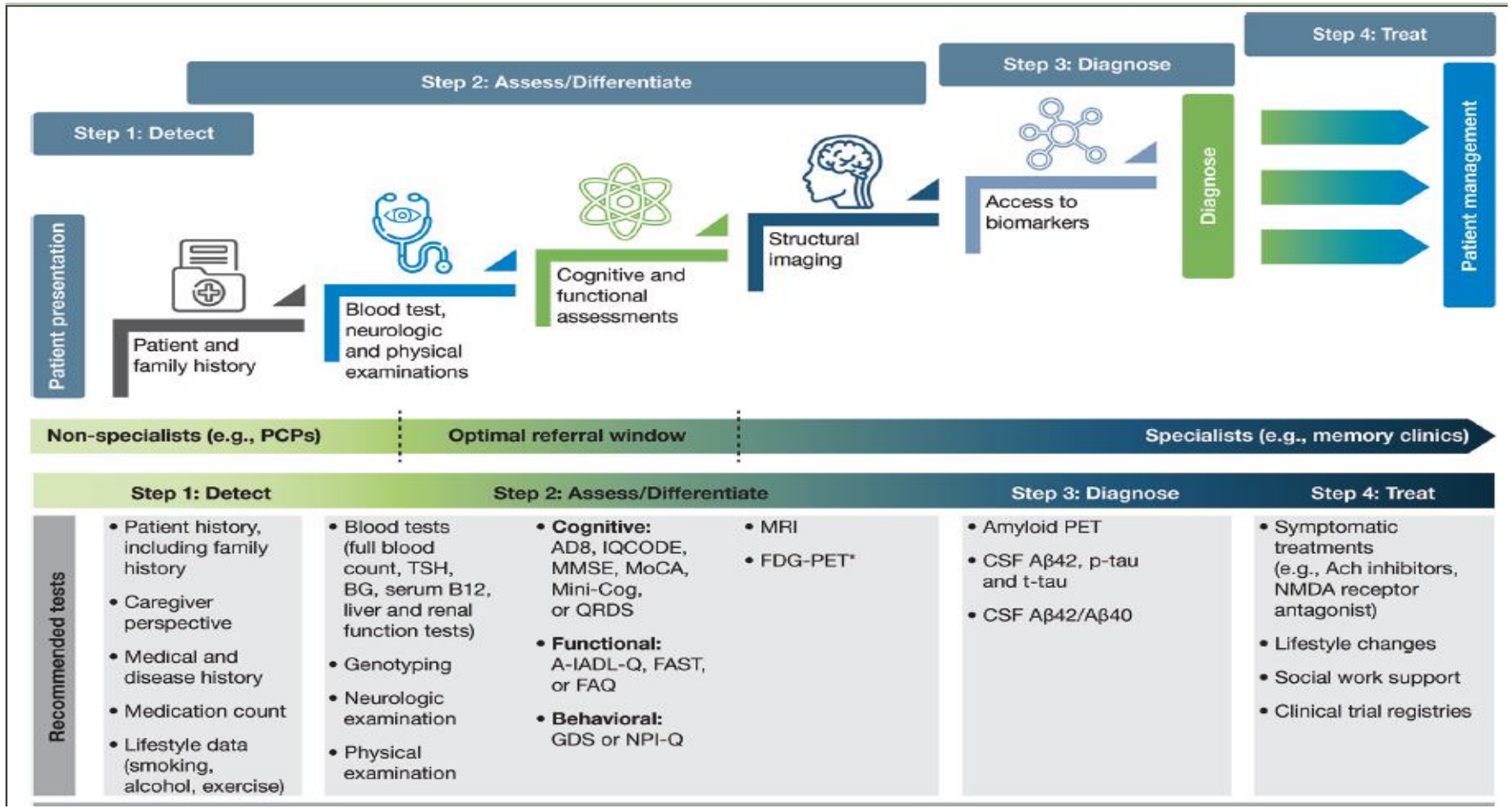
Antipsychotic agents

- Symptoms that may respond to antipsychotic medication include physical aggression and psychotic symptoms. They should be used for the shortest time possible, at the lowest dose possible.

Antidepressants

- Selective serotonin reuptake inhibitors are used as the first-line treatment because of their favorable side-effect profile and because an antidepressant with strong anticholinergic effects may worsen cognition.

A Stepwise Infographic to Highlight Key Stages Within The Diagnostic Process, Along With The Recommended Tests To Support Each Step



Case study

- A 56-year-old business man visited the specialist clinic accompanied by his wife, having been referred by his GP for evaluation of memory loss
- He presents with a history of an insidious onset of cognitive difficulties that have been progressive over the **past 3 years**.
- At work, he has uncharacteristically confused orders and misplaced items, but has no difficulty keeping track of time, and his math, reading, and writing are intact.

Case study: Cont.

- Word finding and literacy skills were noted to have deteriorated in the preceding 6 months according to his wife
- The patient's basic activities of daily living are intact, but more complex instrumental activities of daily living are showing erosion.
- He still drives, but no longer wants to drive to areas he is not familiar with
- He presents with no gait difficulty or balance problems.

Case study: Cont.

- In terms of neuropsychiatric symptoms, his mood is more labile.
- He does have some mixed neuropsychiatric symptoms with intermittent depressive symptoms and anxiety as well as irritability.
- Past medical history significant for hypertension, dyslipidemia, mild obesity, and glucose intolerance.

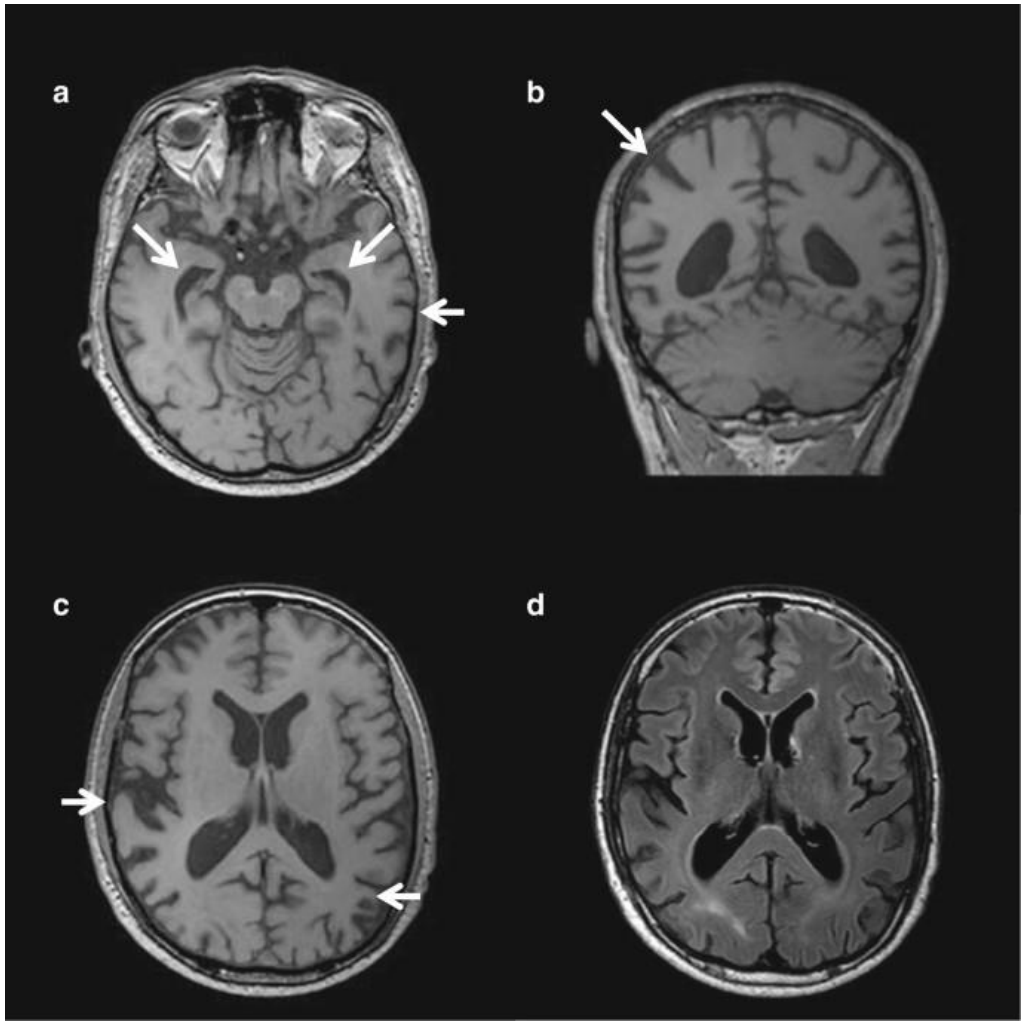
Case study: Cont.

- No history of neurotoxic exposure, head injuries with post-concussion syndrome, strokes, or seizures.
- A positive family history of dementia with his father and paternal grandmother, where onset occurred in the late 60s.

Case study: Cont.

- His general physical examination was unremarkable and there was no focal neurological deficit.
- Neurocognitive assessment revealed a Mini Mental State Examination (MMSE) score of 16/30; poor verbal fluency as well as poor visuospatial and executive skills.

MRI(Brain) – Greater Posterior (Parietal, Temporoparietal Junction) Neocortical atrophy



Case study: Discussion

- In the present case, we discuss a 56-year-old male patient who sought medical help for progressive word-finding difficulties, forgetfulness, agitation and social withdrawal. His history indicated chronicity of (3) years.
- Starting with some difficulties in naming things & people -- **progressive cognitive deterioration**, a key characteristics od dementia.

Case study: Discussion: Cont.

- **Family H/O** similar condition (+)
- Metabolic distuebances , Head trauma, Alcoholism, Drug misuse, Vit deficiencies (-)
- Given the history, physical examination findings and brain imaging findings

↓

Early-onset progressive cognitive deterioration.

Diagnosis

Early Onset Dementia probable due to Alzheimer's disease

Differential Diagnosis of Early-Onset Dementia

- Delirium
- Amnesic syndromes: Korsakoff's syndrome, Anoxic brain damage, Herpes simplex encephalitis
- Pseudodementia: Depression, Dissociative
- Traumatic brain injury
- Neurological illness (e.g. normal-pressure hydrocephalus, stroke, encephalitis, vasculitis, multiple sclerosis)
- General medical conditions (e.g. endocrine, B12 deficiency, systemic lupus erythematosus, sarcoidosis)
- Drugs (e.g. alcohol, benzodiazepines)

Causes of EOD

Primary Neurodegenerations

- **Alzheimer's disease**
- **Frontotemporal lobar degeneration**
- **Dementia with Lewy bodies**
- **Parkinson's disease**
- **Progressive supranuclear palsy**
- **Huntington's disease**

Vascular

- **Vascular dementia (e g, strategic infarct)**

Inflammatory

- **MS, Cerebral vasculitis, neurosarcoidosis, Bechet's disease, vasculitis associated with systemic disorders**

Metabolic

- **Endocrinopathies, Nutritional deficiency, uremia, Hepatic encephalopathy)**

Causes of EOD

Infection

- **Tuberculous/fungal/atypical meningitis)**
- **HIV (AIDS-dementia complex), Neurosyphilis**
- **Whipple disease, Lyme disease, Herpes encephalitis SSPE, PMLE**

Toxic (including CO poisoning, lead, post irradiation)

Chronic alcoholism & chronic drug abuse

Neoplastic/Paraneoplastic

- **Tumors (esp. frontal/callosal/midbrain)**
- **Limbic encephalitis**

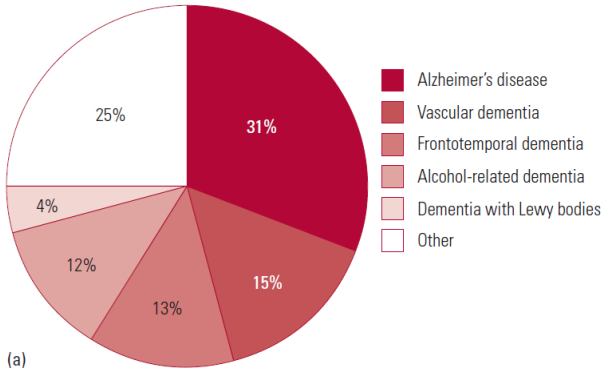
Epilepsy

Prion (classical/iatrogenic CJD)

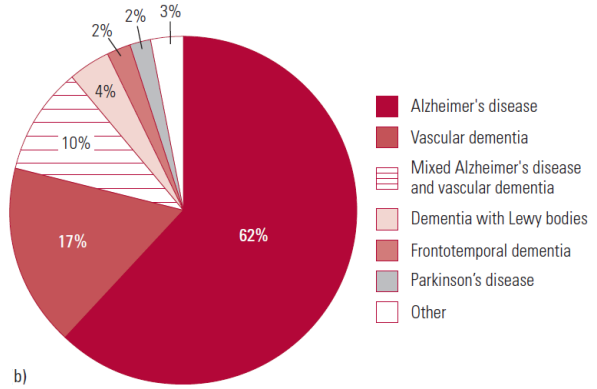
Others - Traumatic brain injury, OSA, Chronic SDH, Hydrocephalus (any cause), Wilson's disease

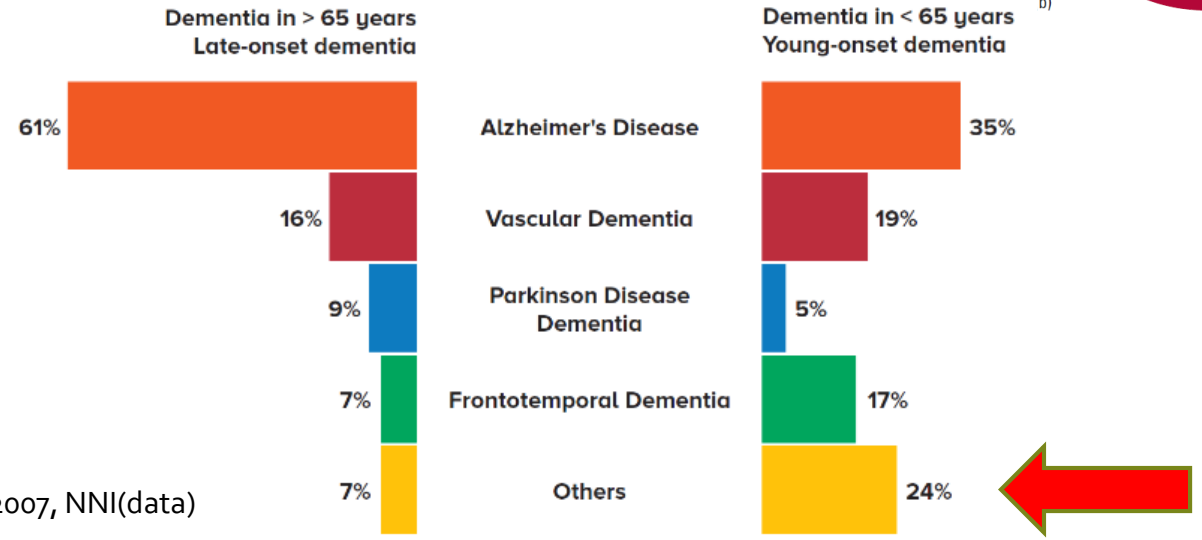
Distribution of diagnoses in Early-onset dementia Versus Late-onset dementia

Early onset dementia



Late onset dementia





Sampson et al 2004, Knapp & Prince 2007, NNI(data)

Reversible Causes

D = Delirium

E = Endocrine disease (Hypothyroidism)

M = Metabolic disturbances
(Hepatic/Renal Insufficiency, Wilson's disease)

E = Eye & Ear impairments

N = Nutritional disorders(Deficiency of Vitamin B12, Thiamine, Niacin), NPH

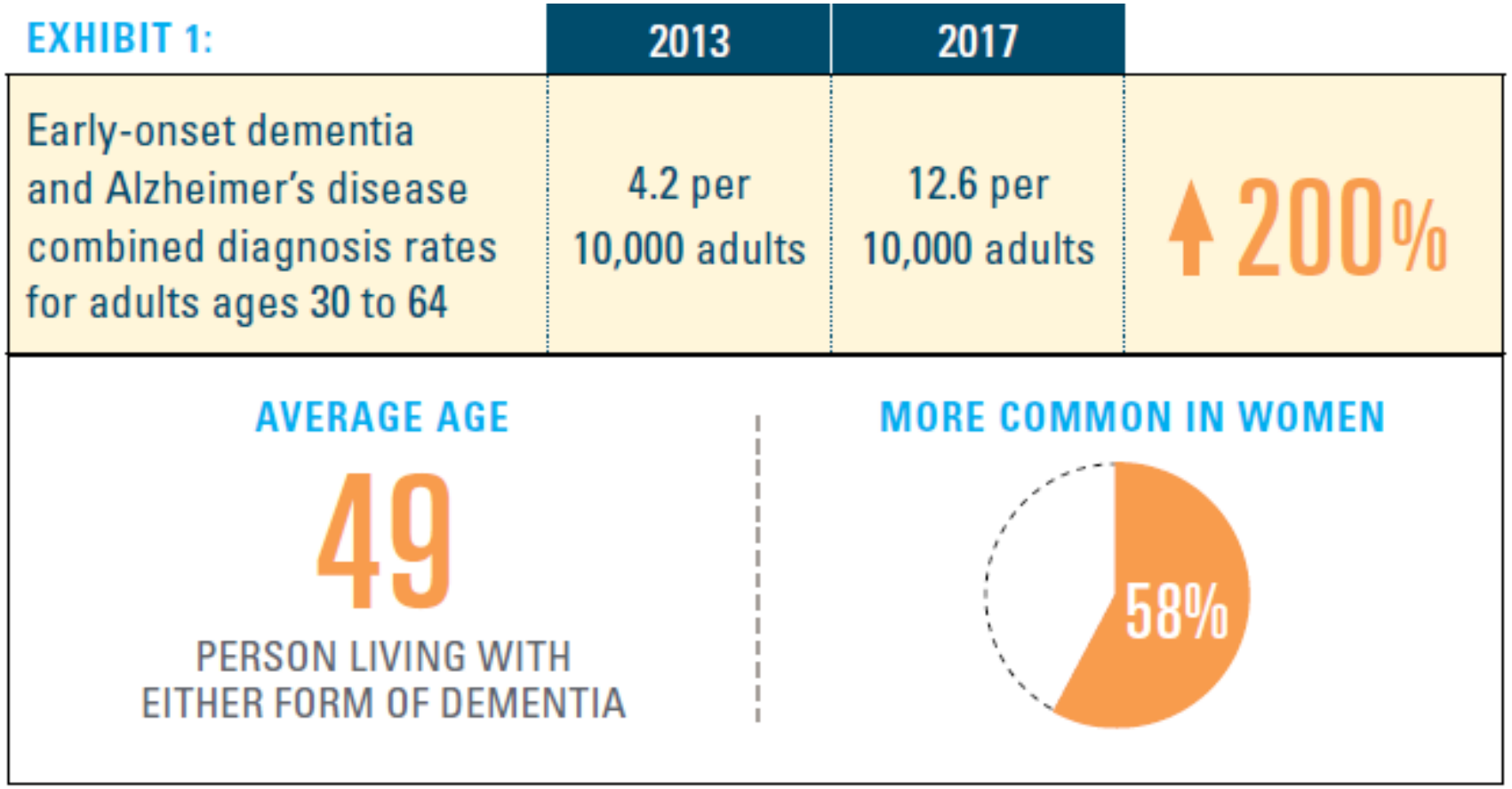
T = Tumors, Toxicity(Heavy metals), Trauma(Subdural Haematoma)

I = Infectious disorder(HIV, Neurosyphillis, Cryptococcus)

A = Alcohol, Atherosclerosis

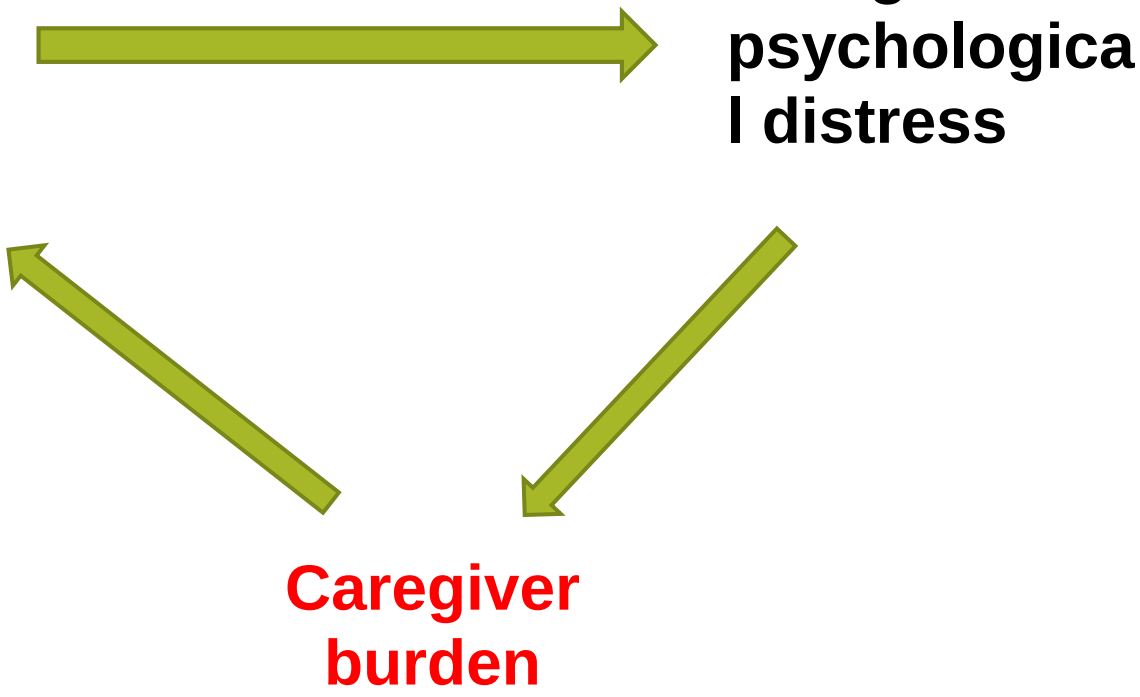
Burden of EOD

Early-Onset Dementia and Alzheimer's Disease affects a growing number of younger Commercially Insured Americans



Burden of EOD

- Disease duration
- Diagnostic delay
- Behavioural and Psychological Symptoms of Dementia (BPSD)
- Patient QoL
- Patient education
- Social network
- Caregiver age
- Spouse caregiver
- Financial distress
- Day off work
- Spousal relation



Challenges IN EOD

- **Difficulty getting an accurate diagnosis**
- **Loss of employment and job-related Income**
- **High out-of-pocket expenditures for long-term Care**
- **Lack of appropriate medical care, residential care, and community services**

Conclusion

- EOD - More aggressive course with high rate of mortality
- Overall less semantic memory impairment and greater attention, executive, praxis, and visuospatial difficulties
- Greater psychosocial problems

Conclusion Cont.

- Suspicious index for dementia at a young age is low representing a diagnostic challenge given the low presence of key manifestations, unspecific symptoms and the younger age at presentation

- Burden
  - ✓ Early-onset dementia and Alzheimer's disease affects a growing number of younger

- Challenges
  - ✓ Difficulty getting an accurate diagnosis
  - ✓ Loss of employment and job-related Income

Conclusion Cont.

- ✓**STEPS TO REDUCE THE PROBLEMS**
  - ✓ **Increase** awareness of early onset dementia and the importance of accurate diagnosis among doctors and other health care professionals.
  - ✓ **Provide** training for doctors about how to diagnose early onset dementia
  - ✓ **Increase** awareness of early onset dementia among employers and human resources personnel
  - ✓ **Provide** information about possible work accommodations for people with early onset dementia

Thanks For Your Attention