COMMENTARY

Dementia

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Introduction

Dementia refers to a disease process marked by progressive cognitive impairment in clear consciousness. According to the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), dementia is the development of multiple cognitive deficits manifested by both memory impairment and impairment in at least one other cognitive domain including language, praxis, gnosis and executive functioning. Alzheimer's disease (AD) and other dementias incur huge costs to society, to the families of those affected, and to the individuals themselves. As the population ages, these costs pose substantial social and economic problems.

History

The word dementia derives from the Latin word 'dementatus' meaning "out of one's mind". Celsus first used the term 'dementia' in the 1st century A.D. Oribasius in the 4th century A.D. wrote of a disease of cerebral atrophy that caused loss of intellectual capacity and weakness of movement. In the 19th century Jean Etienne Dominique Esquirol wrote “Mental Maladies: A Treatise On Insanity”. In 1845 Wilhelm Griesenger first described senile dementia as a disease of cerebral arteries. In 1907 Alois Alzheimer first identified specific histopathological changes associated with progressive degenerative dementia.

Classification

1. Dementia of the Alzheimer’s type
   Early onset: uncomplicated, with delirium, with delusions, with depressed mood
   Late onset: uncomplicated, with delirium, with delusions, with depressed mood
2. Vascular dementia: uncomplicated, with delirium, with delusions, with depressed mood
3. Dementia due to head trauma
4. Dementia due to Parkinson’s disease
5. Dementia due to HIV disease
6. Dementia due to Huntington’s disease
7. Dementia due to Pick’s disease
8. Dementia due to Cruetzfeldt-Jakob disease
9. Dementia due to other general medical conditions
10. Substance induced persisting dementia
11. Dementia due to multiple aetiologies
12. Dementia not otherwise specified

Epidemiology

Dementia is already epidemic and one of the top ten causes of disability in developed countries (Murray and Lopez 1997). World Health Organization (WHO) projections suggest that by 2025, about three quarters of the estimated 1.2 billion people aged 60 years and older will reside in developing countries. Thus, by 2040, 71% of 81.1 million dementia cases will be in the developing countries. About 4.6 million new cases of dementia are added every year, with the highest growth projections in China and its South Asian neighbours. Dementia prevalence in 65 years old in India and Sub-Saharan Africa are low (1-3%) than some other Asian and Latin American countries (>= 5%). Dementia costs in developing countries are estimated to be 73 billion dollars yearly. Prevalence doubles about every five years from about 5-8% at the age of 65-70 years to 15-20% at age 75-80 years and upto 40-50% over age 85 years. Alzheimer’s disease constitutes 50-75%, dementia with Lewy bodies 15-35% and vascular dementia 5-20%.

Aetiology

1. Neurodegenerative: Alzheimer’s disease, dementia with Lewy body, frontotemporal dementia, Parkinson’s disease, Huntington’s disease.
2. Vascular: Infarction, Binswanger’s disease, haemodynamic insufficiency.
3. Neurological disease: Multiple sclerosis, amyotrophic lateral sclerosis, normal pressure hydrocephalus, brain tumours (primary or secondary), recurrent nonconvulsive seizures.
4. Endocrine: Hypothyroidism, hypercalcaemia, hypoglycaemia, Cushing’s syndrome, hypo/hyperparathyroidism.
5. Nutritional: Vitamin B12, niacin, thiamine deficiency.
6. Infectious: HIV, prion disease, neurosyphilis, cryptococcus.
7. Metabolic: Hepatic insufficiency, renal insufficiency, pulmonary failure, Wilson’s disease, acute intermittent porphyria.
8. Traumatic: Subdural haematoma, dementia pugilistica.
9. Exposure.

Evaluation

1. History: Antecedent history, psychiatric history, nature and evolution of symptoms, family history, social history.

2. Examination

3. Psychometric testing: Mini mental state examination (MMSE) – most widely employed tool for basic screening and evaluation. Functions which are to be assessed include – premorbid ability, attention, orientation, visual, auditory and tactile recognition, visuospatial skills, perception, language comprehension (oral and reading), language expression (repetition, fluency, naming, writing), recognition (verbal, non-verbal, spatial information), learning (verbal, non-verbal, spatial information), recall (verbal, non-verbal, spatial information), executive function, cognitive speed, praxis.

4. Imaging: Structural and functional imaging.

5. Electroencephalography (EEG)

6. Laboratory studies

7. Neuropathological studies

Clinical features

1. Cognitive impairment: Memory impairment, aphasia or language impairment, apraxia, agnosia, impairment in executive functioning.

2. Functional impairment

3. Neuropsychiatric manifestations: Behavioural disturbance, mood changes, anxiety, personality changes, psychosis, sleep disturbance.

Differential diagnosis

1. Delirium: Altered level of consciousness with the cognitive impairment, onset generally sudden and acute, fluctuating level of alertness, attention is the hallmark cognitive domain impaired, usually precipitated by one or more, and usually a combination of factors.

2. Mild cognitive impairment: Memory complaint, objective memory impairment for age and education, preserved general cognitive function, intact activities of daily living, not demented.

3. Amnestic disorders: Memory impairment is the core symptom, no global intellectual decline, or impairment of attention and clouding of consciousness.

4. Age-related cognitive decline

5. Benign senescent forgetfulness

6. Malignant senescent forgetfulness

7. Age associated memory impairment

8. Depression/pseudodementia

9. Schizophrenia

10. Mental retardation

11. Factitious disorders

Dementia subtypes

1. Alzheimer's disease is the most common type of dementia.

Epidemiology: Incidence increases with age -

0.5%	- 65-69 yrs.
1%	- 70-74 yrs.
2%	- 75-79 yrs.
3%	- 80-84 yrs.
8%	- after age 85.

Aetiology

A. Genetics

Early onset disease: Autosomal dominant, mutations in three genes - amyloid precursor protien (APP), located in chromosome 21; presenilin-1 (PS-1), located in chromosome 14; presenilin-2 (PS-2), located in chromosome 1. PS-1 mutations are seen in 20% of cases, PS-2 and APP mutations account for 1% and 5% of cases respectively.

Late onset disease: Only one gene, apolipoprotien E gene (APOE) located on chromosome 19 is implicated. It has three alleles – E2, E3 and E4. The risk of Alzheimer's disease increases and the mean age of onset is earlier as the number of E4 allele increases from 0 to 2. The APOE gene accounts for only 50% of Alzheimer's disease cases.

B. The cholinergic hypothesis: There are relatively greater and earlier loss of cholinergic neurotransmission. Postmortem findings show greater neuronal loss in the cholinergic nucleus basalis of Meyernet and loss of cholinergic markers. The activity of choline acetyltransferase is substantially reduced. Cholinergic hypothesis states that cognitive impairment in schizophrenia was due to a disorder predominantly affecting cholinergic neurons.

C. Amyloid beta protein and synapse loss

D. Other possible aetiological factors: Age, education, head trauma, inflammation, oxidative stress.

Pathology and laboratory examination: Macroscopically, early disease may appear normal or atrophy confined to the hippocampus. In advanced disease, widened sulci throughout the cortex and increased ventricular size are seen. Posterior temporal, parietal and frontal lobe atrophy are most prominent.

Microscopically, characteristic lesions are amyloid plaques and neurofibrillary tangles. Amyloid plaques are defining lesions of Alzheimer's disease. They are found throughout the neocortex, etorhinal cortex, hippocampus and subcortical regions. Neurofibrillary tangles are intracellular inclusion bodies containing paired helical filaments composed of aggregates of hyperphosphorylated microtuble associated protein tau (MAPT). They are found more in entorhinal cortex, hippocampus and lateral temporal lobe than the neocortex.

Additional pathological features: Neuronal loss is most marked in the entorhinal cortex and hippocampus. In later disease, there are loss of cholinergic neurons in the nucleus basalis, loss of brainstem noradrenergic and serotonergic neurons. There is abnormal aggregation of alpha synuclein. Granulovacuolar degeneration and the presence of Hirano bodies, most commonly affecting pyramidal neurons in the hippocampus are seen.

Course and prognosis: Generally patients present with a gradual decline in short time memory and language function. Gradually progressive decline in cognitive function extends to all cognitive domains. On average, the MMSE score will decline by about three points per year. In final stages, there are Parkinsonian symptoms, gait disturbances and mobility impairment. Eventually patients will be bedridden and often succumb to pneumonia or other infections.

2. Vascular dementia refers to cognitive decline caused by ischaemic, haemorrhagic or oligaemic injury to the brain as a consequence of cerebrovascular or cardiovascular disease. It is a part of a spectrum of vascular disease causing cognitive impairment. Kraepelin first described 'arteriosclerotic dementia' in 1896. Haschinski, in the 20th century, described 'multi-infarct dementia'. Now it refers to three subtypes – cortical, subcortical and strategic infarct.

Risk factors are age, evidence of vascular disease, hypertension, diabetes, apolipoprotien E4 allele, hyperlipidemia, peripheral artery disease, smoking.

Aetiology are stroke, small vessel ischaemic disease, haemorrhage, subdural haematoma, epidural haematoma, intraparenchymal haemorrhage, chronic hypoperfusion, congestive cardiac failure, cardiac arrhythmias, cerebral amyloid angiopathy.

Diagnosis is by cognitive deficits, focal neurological signs and symptoms, and evidence of cerebrovascular disease that can be aetiologically related to the cognitive deficits.

Clinical features: In cortical, onset is acute. Cognitive deficits reflect losses that map to the region of stroke. Memory impairment and loss of executive control and information processing are most common. Typical neurological signs and symptoms of cortical strokes are lower facial weakness, upper motor neuron lesions, and gait abnormalities. Course is stepwise progression with plateaus, with further decline being related to subsequent strokes.

In subcortical, onset is slow insidious. One third of patients have acute onset. Subtle focal signs include gait disorder, imbalance and urinary incontinence. Dysexecutive syndrome, mental slowing and reduced ability to set and reach goal. Memory loss may be minor. Depression, emotional lability and personality change may occur. \

Strategic infarct has acute onset. At least 30% of individuals above age 70 years will develop 'poststroke dementia'. Memory impairment is mild to severe. Associated symptoms are apathy, loss of spontaneity, perseveration, and fluctuating consciousness and confusion.

Pathology and laboratory examination: No clear pathological changes are diagnostic of vascular dementia.

Differential diagnosis: Alzheimer's disease with cerebrovascular disease, frontotemporal dementia.

Course and prognosis are dependent on the nature, extent and course of the vascular disease that causes it.

3. Dementia with Lewy body (DLB) is a neurodegenerative dementia characterized by progressive cognitive decline of sufficient severity to interfere with normal social or occupational function. Memory impairment is not prominent early in the course of disease. It was first described in 1986 by Kosaka. DLB occurs more frequently in males, with the average onset at age 75 to 80 years. Clinically, distinguishing DLB from AD or Parkinson's disease with dementia (PDD) can be difficult because these conditions have a number of features in common. Clinical and neuropathological diagnostic criteria were published by the Consortium on Dementia with Lewy Bodies in 1996 and revised in 2005.

Aetiology: Mutations in alpha synuclein (SNCA) and beta synuclein (SNCB) genes.

Clinical features: Cognitive impairment consisting of forgetfulness (retrieval more impaired than recognition memory), apathy, psychomotor slowing, impairments of attention, visual-spatial impairments, subcortical dementia features, increased risk of delirium.

Neuropsychiatric features are hallucinations, delusions, behavioural dysregulation, agitation, aggression, nocturnal wandering, disinhibition,

depression, emotional lability, pseudobulbar affect, anxiety, obsessive/compulsive.

Motor dysfunction includes extrapyramidal features, typically symmetric akinetic-rigid form of parkinsonism with mild to moderate rigidity and bradykinesia, typically not a classic asymmetric resting tremor, mild symmetric postural and kinetic tremor is common.

Sleep disorders like rapid eye movement (REM) sleep behaviour disorder, insomnia, restless legs syndrome, periodic limb movements of sleep, excessive daytime sleepiness.

Autonomic dysfunctions are orthostatic hypotension, poorly regulated sweating, poorly regulated body temperature, dry skin, decreased ventilatory response to hypercapnia, incontinence, detrusor hyperactivity, erectile dysfunction, constipation, gastroparesis, cardiac arrhythmias.

Pathology and laboratory examination: The pathology of DLB closely resembles that of Parkinson's disease. Patients with DLB are characterized by the diffuse presence of Lewy bodies in both subcortical and cortical areas of the brain whereas Parkinson's disease patients have Lewy bodies in the subcortical areas of the brain mainly substantia nigra and locus coerules (LC). Both DLB and Parkinson's disease are associated with abnormal aggregation of SNCA which is a nerve terminal protein. Biochemically, numerous neurotransmitters, including acetylcholine (ACh) and dopamine (DA) are diminished in DLB. The decrease in ACh may be more severe than in AD.

Pathological features in DLB are diffuse Lewy bodies (essential for diagnosis of DLB), Lewy neuritis, senile plaques (all morphological types), neurofibrillary tangles, neuronal loss in substantia nigra, neuronal loss in LC, Meynert nucleus neuronal loss, microvacuolation and synapse loss, neurochemical abnormalities and neurotransmitter deficits e.g. ACh, DA.

Imaging: Regionally distinct patterns of hypoperfusion on single-photon emission computed tomography (SPECT) or hypometabolism on positron emission tomography (PET) and DAergic loss in the basal ganglia can differentiate DLB from other dementias. Reduced dopamine transporter (DAT) activity in the basal ganglia is seen with PET or SPECT scanning. DaTSCAN (Ioflupane, 123-I FP-CIT) SPECT is indicated for detecting loss of functional DAergic neuron terminals in the striatum. The sensitivity of the FP-CIT scan for the diagnosis of DLB is 88% and specificity is 100%. It helps to differentiate probable DLB from AD.

Differential diagnosis of DLB: AD, Parkinson's disease, PDD, psychiatric illnesses like mania and psychotic depression, vascular dementia, delirium.

Course and prognosis: DLB may have a more rapidly progressive course than AD or vascular disease. Survival time is usually ten years, although it may be as little as one to two years. The course is often marked by psychosis and behavioural disturbance, which makes the management more complicated.

4. Frontotemporal dementia: Predominant clinical syndrome associated with these group of dementias is characterized by progressive circumscribed atrophy of frontal and temporal lobe cortices, identified as frontotemporal lobar degeneration. Arnold Pick in the late 19th and early 20th century provided the initial descriptions of the clinical syndrome of a dementia with associated circumscribed atrophy of the frontal and temporal lobes. Three broadly accepted subgroups are the frontal or behavioural variant, primary progressive aphasia, and semantic dementia.

Epidemiology:

More likely to affect younger populations. Age on onset is 35-75 years. Mean age of onset is sixth decade. No clear relationship to gender.

Aetiology:

Sporadic form is of unknown etiology. In the familial form, there are mutations in proganulin gene (GRN) located in chromosome 17, mutations in MAPT gene located in chromosome 17, mutations in chromatin modifying protein 2B (CHMP2B) and vasolin containing protein (VCP).

Pathology:

Macroscopically, focal atrophy of frontal cortex, temporal cortex, or both. Atrophy is usually symmetric. Microscopically, frontotemporal lobar degenerations can be divided into two major groups - (a) Tau positive inclusions – classical Pick's disease, and (b) Tau negative and ubiquitin positive inclusions – presence of intracellular inclusions containing TDP-43 - most cases of frontotemporal lobar degeneration. Cases with ubiquitinated lesions without TDP-43 have been recently identified, which appear to have abnormal deposits of another protein called fused in sarcoma protein (FUS).

Clinical diagnostic features of frontotemporal dementia :

Core diagnostic features: Behavioural disorder having insidious onset and slow progression, early loss of personal awareness (neglect of personal hygiene and grooming), early loss of social awareness (lack of social tact, misdemeanours), early signs of disinhibition (such

as unrestrained sexuality, violent behaviour), mental rigidity and inflexibility, hyperorality, stereotyped and perservative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing), utilization behaviour (unrestrained exploration of objects in the environment), distractibility, impulsivity, and impersistence, early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms like depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion, hypochondriasis, bizarre somatic preoccupation (early and evanescent), emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy), amimia (inertia, aspontaneity).

Speech disorder such as progressive reduction of speech (aspontaneity and economy of utterance), stereotypy of speech (repetition of limited repertoire of words, pharases, or themes), echolalia.

Spatial orientation and praxis are preserved (intact abilities to negotiate the environment).

Physical signs include early primitive reflexes, early incontinence, late akinesia, rigidity, tremors, low and labile blood pressure.

Investigations: Normal EEG despite clinically evident dementia, brain imaging (structural or functional, or both) showing predominant frontal or anterior temporal abnormality, or both. Neuropsychology reveals profound failure on 'frontal lobe' tests in the absence of severe amnesia.

Supportive diagnostic criteria are onset before 65 years, positive family history of similar disorder in a first degree relative, bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

Diagnostic exclusion features include abrupt onset with ictal events, head trauma related to onset, early severe amnesia, early spatial disorientation, lost in surroundings, defective localisation of objects, early severe apraxia, logoclonic speech with rapid loss of train of thought, myoclonus, cortical bulbar and spinal deficits, cerebellar ataxia, choreo-athetosis, early, severe, pathological EEG, brain imaging showing predominant post-central structural or functional deficit, multifocal cerebral lesions on CT or MRI or laboratory tests indicating brain involvement or inflammatory disorder such as multiple sclerosis, syphilis, acquired immunodeficiency syndrome (AIDS) and herpes simplex encephalitis.

Relative diagnostic exclusion features are typical history of chronic alcoholism, sustained hypertension, history of vascular disease (such as angina, claudication).

Differential diagnosis includes other psychiatric disorders like bipolar disorder, major depression and late onset schizophrenia, AD with predominant frontal presentation, DLB with combination of cognitive impairment and parkinsonism.

Course and prognosis: Progressive deterioration. With progression the differing initial presentation merge.

Management of dementia

A. Pharmacological treatment

(i) Psychosis and behavioural disturbance: Antipsychotics like risperidone, olanzepine, quetiapine and aripiprazole. Clozapine in Parkinson's disease and DLB. Modest but clinically significant improvements in measures of agitation, aggression and behavioural disturbance. Benzodiazepines, anticonvulsants, selective serotonin reuptake inhibitor (SSRI), others such as trazodone.

(ii) Depression: SSRI like citalopram, fluoxetine and sertraline.

(iii) AD: Cholinesterase inhibitors, memantine.

(iv) Vascular dementia: Primary prevention, secondary prevention, cholinesterase inhibitors, memantine.

(v) DLB: Cholinesterase inhibitors are first line for both cognitive deficits and psychosis, antiparkinsonian medications.

(vi) Frontotemporal dementia: No treatments for the cognitive deficits associated with this condition or to prevent progression of the underlying pathologies.

B. Nonpharmacological treatment: Psychosocial interventions, psychotherapy, behavioural management, cognitive retraining, stimulation–oriented therapy, education, legal and financial issues, maintaining safety, driving, caregiver support, end-of-life issues.

Recent advances

1. The sirtuin pathway in ageing and AD: mechanistic and therapeutic considerations.

2. Biomarkers in AD: Plasma - α2-macroglobulin, complement factor H, Aβ42; cerebrospinal fluid (CSF) - Aβ42, t-tau, p-tau p-tau/Aβ42, t-tau/Aβ42; neuronal biomarkers in CSF - visinin-like protein 1 (VLP-1), synaptic protein called growth-associated protein (GAP-43), neurofilaments.

3. Advances in tau-focused drug discovery for AD and related tauopathies.

4. Potential treatments for FTD based on recent genetic discoveries about the illness:

Mutation	Mechanism of potential treatment	Example
PGRN	Progranulin/granulin supplementation Immunosuppression Inhibition of TDP-43 aggregation	FK506
MAPT	Glycogen synthase kinase-3 inhibition Microtubule stabilization	Lithium Valproate Paclitaxel

5. DAergic treatments for FTD: DAergic enhancers like amantadine, tolcapone.

Conclusion

For the foreseeable future, dementia will remain a disorder afflicting a large proportion of the world's elderly. The impact on developing countries will be considerable. As the molecular pathology of dementia is increasingly understood, it is to be hoped that this is translated into treatments ever more effective in modifying or preventing the disease process itself.

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