INTRODUCTION

Dementia is a syndrome due to disease of the brain – usually of a chronic or progressive nature – in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension and judgement due to disease of the brain. The common causes are Alzheimer’s disease, vascular dementia and other neurodegenerative diseases. As the world population is growing older day by day, the incidence of dementia is also increasing in its full pace. Dementia is also, one of the major causes of disability in later life. It accounts for 11.9% of the years lived with disability due to a non-communicable disease in people aged 60 years and older. Hence, its impact on financial, social and psychological status of patients and their caregivers cannot be ignored and finding a novel way to tackle these health problems is the need of present times.

Keywords: Dementia, Alzheimer’s disease, neurodegenerative diseases, memory, disability in later life.

ABSTRACT

Dementia is a syndrome, usually chronic, characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgement due to disease of the brain. The common causes are Alzheimer’s disease, vascular dementia and other neurodegenerative diseases. As the world population is growing older day by day, the incidence of dementia is also increasing in its full pace. Dementia is also, one of the major causes of disability in later life. It accounts for 11.9% of the years lived with disability due to a non-communicable disease in people aged 60 years and older. Hence, its impact on financial, social and psychological status of patients and their caregivers cannot be ignored and finding a novel way to tackle these health problems is the need of present times.

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Dementia is a syndrome, usually chronic, characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgement due to disease of the brain. The common causes are Alzheimer’s disease, vascular dementia and other neurodegenerative diseases. As the world population is growing older day by day, the incidence of dementia is also increasing in its full pace. Dementia is also, one of the major causes of disability in later life. It accounts for 11.9% of the years lived with disability due to a non-communicable disease in people aged 60 years and older. Hence, its impact on financial, social and psychological status of patients and their caregivers cannot be ignored and finding a novel way to tackle these health problems is the need of present times.

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100,000 females. For India and WHO SEARO D-sub region, the dementia mortality rate is 13.5 per 100,000 males and 11.1 per 100,000 females. Compared to other chronic medical conditions (heart diseases, cancer and stroke), AD is the fourth leading cause of death in the Asia Pacific region.4,5

Diagnosis of dementia:

Dementia is caused by various diseases and conditions that result in damaged brain cells. To diagnose someone with dementia, the following criteria is widely used:9

A) A decline in memory and in at least one of the following cognitive abilities:
- Ability to generate coherent speech or understand spoken or written language;
- Ability to recognize or identify objects, assuming intact sensory function;
- Ability to execute motor activities, assuming intact motor abilities, sensory function and comprehension of the required task; and
- Ability to think abstractly, make sound judgments and plan and carry out complex tasks.

B) The decline in cognitive abilities must be severe enough to interfere with daily life.

Two main types of criteria are used for diagnosis of dementia in India:

1) The DSM-IV criteria (The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition), developed by American Psychiatry Association.10
2) The 10/66 dementia diagnosis: This criterion relies on an algorithm which was validated in an extensive pilot study conducted in India and other countries. It has an overall sensitivity of 94% and a specificity of 97% for those with higher and 94% for those with lower levels of education.7,11

Course and outcome of dementia:

The symptoms and problems linked to dementia can be best understood in three stages:2

1) Early stage (developed in 1-2 years): The early stage of dementia is often overlooked because the onset of dementia is gradual. The person may have problems in talking properly (language problems) or have significant memory loss – particularly for things that have just happened or not know the time of day or the day of the week.
2) Middle stage (developed in second to fifth year): As the disease progresses, limitations become clearer and more restricting. The person with dementia has difficulty with day-to-day living and may become very forgetful – especially of recent events and people’s names or can no longer manage to live alone without problems or unable to cook, clean or shop.
3) Late stage (developed in fifth year or after): This stage is one of near total dependence and inactivity. Memory disturbances are serious and the physical side of the disease becomes more obvious. The person may have difficulty eating, be incapable of communicating, not recognize relatives, friends and familiar objects, display inappropriate behavior in public and may become confined to a wheel chair or bed.

There is impairment in short term and long term memory, particularly the inability to learn and recall new information. Problems with abstract thinking and judgement occur, as well as the loss of higher cortical functions causing language difficulties, motor impairments, problems with recognition, and personality changes. Eventually, neurological destruction affects all bodily systems, and people generally die of illnesses of debility such as pneumonia (Lezak et al., 2004:207).12

In low and middle income countries, diagnosis is often much delayed, and survival is less than 5-7 years.13

Aetiology & Risk factors:

Advanced age remains the main risk factor for most forms of dementia, with prevalence roughly doubling every five years over the age of 65 in India.5

Onset before 65 year of age is rare and, in the case of Alzheimer’s disease (AD), often suggests a genetic cause. Single gene mutations of either β-amyloid precursor protein or presenilin-1 or presenilin-2, account for most of the cases of early onset AD.14,15

For late-onset of AD, both environmental (lifestyle) and genetic factors are important. A common genetic polymorphism, the apo-lipoprotein E (apoE) gene e4 allele, greatly increases the risk of dementia. Up to 25% of the population has one or two copies of this allele.14,15

The evidence strongly establishes a causal role of cardiovascular risk factors and cardiovascular disease in the aetiology of dementia and AD. Those with high cardiovascular risk scores (incorporating hypertension, diabetes, hypercholesterolemia and smoking) have an increased risk for dementia.16 Recent studies support the associations between metabolic syndrome and cognitive decline, and also between insulin resistance and impaired executive function.17 Diabetes, hypertension and hypercholesterolemia are also associated with the onset of AD. Depression, head injury, limited education etc. is found to be associated with AD in a few studies, but strong evidences are lacking.18,19

Neuropathology of dementia:

Dementia is not a disease but is a syndrome of progressive cognitive decline caused by numerous different pathologies. In early stages cognitive symptomatology differs with different aetiologies, however as neurodegenerative pathology progresses, then the marked destruction of brain tissue produces similar symptoms whatever be the cause.15

Macroscopically, brain is atrophic resulting in secondary enlargement of ventricles. Atrophy occurs in specific areas of the brain, including the frontal, temporal and parietal cortex and the hippocampus. Microscopically, Alzheimer Disease is characterized by degeneration of neurons especially synapses and dendrites, along with the presence of β-amyloid (βA) plaques, neurofibrillary tangles (NFTs) and granulovascular degeneration throughout the cortex and sub-cortical grey matter. More
than 50% of AD patients show white matter changes called as selective incomplete white matter infarctions.\textsuperscript{27}

\textbf{β}-amyloid perturbs cellular properties by multiple mechanisms, including induction of oxidant stress by binding and entrapping the metals in the plaque, metals catalyze the conversion of \( \text{H}_2\text{O}_2 \) to hydroxyl radicals (OH\textsuperscript{•}) in excess, challenging cellular antioxidants defenses and redirecting protein synthesis. Oxidant-related activation of the transcription factor-kB (NF-kB), for example, induces expression of cytokines and cell adherence molecules, thereby modulating cell-cell interactions.\textsuperscript{29}

The \textbf{β}-amyloid can bind to specific receptor, such as RAGE (receptor for advanced glycation end products) or type-2-scavenger receptor, may induce free radical production by stimulating the activity of the reduced form of nicotinamide adenine dinucleotide oxidases. The accumulation of excitatory amino acids such as L-glutamate can induce nerve cell death by over activation of specific glutamate receptors or by the induction of oxidative events. The latter are initiated by the competition of glutamate for the neuronal cysteine-antipporter system that in a first step leads to a depletion of intracellular glutathione and in a second step to an accumulation of \( \text{H}_2\text{O}_2 \). The consequences are the peroxidation of membrane lipids by oxidative chain reaction and the lysis of the cells.\textsuperscript{20,21}

There occurs a depletion of the neurotransmitter acetylcholine and the enzyme which produces it- choline acetyltransferase, along with other neurotransmitters and neurochemicals (World Health Organisation, 1992, cited in Henderson & Jorm, 1998). These changes result in diminished cognitive function that worsens as the disease progresses.

### Major types of dementia and their characteristics:\textsuperscript{9}

<table>
<thead>
<tr>
<th>Types of Dementia</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Most common type of dementia; accounts for 60 to 80 percent of cases. Difficulty remembering names and recent events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired judgment, disorientation, confusion, behaviour changes, and trouble in speaking, swallowing and walking. Hallmark abnormalities are deposits of the protein fragment beta-amyloid (plaques) and twisted strands of the protein tau (tangles).</td>
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<tr>
<td>Vascular dementia (also known as multi-infarct dementia or vascular cognitive impairment)</td>
<td>Considered the second most common type of dementia. Impairment is caused by decreased blood flow to parts of the brain, often due to a series of small strokes that block arteries. Symptoms often overlap with those of Alzheimer’s, although memory may not be as seriously affected.</td>
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<tr>
<td>Mixed type</td>
<td>Characterized by the presence of the hallmark abnormalities of Alzheimer’s and another type of dementia, most commonly vascular dementia, but also other types, such as dementia with Lewy bodies.</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>Pattern of decline may be similar to Alzheimer’s, including problems with memory and judgment and behaviour changes. Alertness and severity of cognitive symptoms may fluctuate daily. Visual hallucinations, muscle rigidity and tremors are common. Hallmarks include Lewy bodies (abnormal deposits of the protein alpha-synuclein) that form inside nerve cells in the brain.</td>
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<tr>
<td>Parkinson’s disease</td>
<td>Many people who have Parkinson’s disease develop dementia in the later stages of the disease. The hallmark abnormality is Lewy bodies (abnormal deposits of the protein alpha-synuclein) that form inside nerve cells in the brain.</td>
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<tr>
<td>Fronto temporal dementia</td>
<td>Involves damage to brain cells, especially in the front and side regions of the brain. Typical symptoms include changes in personality and behaviour and difficulty with language. No distinguishing microscopic abnormality is linked to all cases. Pick’s disease, characterized by Pick’s bodies, is one type of front temporal dementia.</td>
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<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Rapidly fatal disorder that impairs memory and coordination and causes behaviour changes. Variant Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease. Caused by the misfolding of prion protein throughout the brain.</td>
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Management of dementia: The standard treatment goals of dementia management include: 2

1) Early diagnosis.
2) Optimization of physical health, cognition, activity and well being.
3) Detection and treatment of Behavioural and Psychological Symptoms of Dementia.
4) Educating care takers and providing long term support to them.
5) Carer interventions such as Psycho-educational interventions, Psychological therapies, e.g. cognitive behavioural therapy (CBT), counselling and Respite care.

Treatment for memory disorders:22,23

The memory can be improved by non pharmacological measures such as simple lifestyle changes like incorporating memory exercises, healthy eating (Omega-3 fatty acids and vitamin rich diets, fish, fruits, vegetables etc.), physical fitness and stress reduction into daily lives.

Pharmacological treatment includes variety of agents, such as Acetylcholinesterase inhibitors (e.g. Galantamine, Donepezil), GABA antagonists (e.g. Suritoxazole- α5 partial inverse agonist), Glutamate activators (e.g. Ampakines, Racetams etc), Serotonergics, they increase
their activity of endogenous neurotransmitters. Anti-depressants, mood stabilizers and antioxidants.

List of drugs used in treatment of dementia

- Precursors to acetylcholine (Ach) - they increase amount of Ach, e.g., choline and Lecithin
- Acetylcholinesterase inhibitors- prevent the breakdown of Ach, e.g. tacrine, galantamine, donepezil, rivastigmine and velnacrine
- Cholinergic agonists e.g., bethnicol- it is a muscarinic agonists
- Neuroprotective drugs like acetyl-carntine- it promotes Ach synthesis
- Anaesthetics e.g. procaine HCl- it is a mild CNS stimulant with weak MAO inhibitory action.
- Chelators e.g. EDTA, Desferioxamine- they help in removal of toxins.
- Nerve growth factors – attenuate the degeneration of remaining cholinergic neurons.
- Neuropeptides e.g. ACTH, Somatostatin – they may enhance the activity of endogenous neurotransmitters.
- Calcium channel blockers e.g. Vasopressin, Nimodipine – they inhibit calcium influx associated with cellular damage.
- Cognition enhancers/Nootropic agents e.g. Piracetam,cycllothiazide, and CX-516 (Ampalex),– they are positive AMPA receptor modulators known as ampakines. They increase AMPA-mediated synaptic responses and enhance long-term potentiation as well as upregulating the production of nerve growth factors such as brain-derived neurotrophic factor (BDNF).

- Psychostimulants e.g. Methyl phenidate, Pemoline, Selegilline – they stimulate CNS & irreversibly inhibit MAO.
- Vasodilators e.g. Cyclandelate, Isoxsuprine, Papaverine – enhance blood flow to the brain.

Although a few specific drugs such as Acetylcholinesterase inhibitors show modest clinical efficacy in AD patients, they do not affect the underlying pathology and this, coupled with strong side effects, results in questionable usefulness of these drugs. There is evidence that these medications can slow the progression of symptoms initially, but don’t change the overall outcome or prognosis (Lopez, et al., 2002). So, the search for effective therapeutic strategies continues.

Newer approaches towards treatment of dementia:

The search for new effective therapies is the need of the hour because of the following reasons: 1) To delay the onset of dementia & to effectively control the disease progression. 2) To control all the pathological aspect of dementia. 3) To reduce the cost burden of dementia management. 4) To improve the safety profile of the drugs. Scarpini et al. (2003) identify three promising areas of research:24

a) Reduction of risk factors- such as oxidative stress, cardiovascular risk factors and inflammation.

b) Neurogenesis promotion- via stem cell transplantation and nerve growth factors.

- Prevention and removal of amyloid plaque via vaccine and chelation agents.

Two important strategies for reduction of the risk factors are:

1) Nutritional approaches (e.g. calorie restriction, consumption of fish, monounsaturated oils and antioxidants, especially vitamins C and E)

2) Use of herbal medicines.

Plant products used in the treatment of memory disorder:25

Plant medicines that reputedly act to improve function of the central nervous system are a promising area for research. They are most likely to offer benefits in the above mentioned ‘reduction of risk factors’ category of therapy, because many phytochemicals from plants are now known to be powerful antioxidants, and many also possess a cholinergic modulation effect and anti-inflammatory actions. This is a significant effect because, as highlighted earlier, cholinergic deficits are a feature of dementia. Some of the important herbs, which have shown positive results in preclinical and clinical trials, are Ginkgo biloba, Bocopa monniera, Withania somnifera, Curcuma longa, Acorus calamus etc.
REFERENCES

3. The Dementia India Report 2010, Published by Alzheimer’s and Related Disorders Society of India (ARDSI), New Delhi 2010:1-6