Neuropsychiatric Symptoms at Menopause

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ABSTRACT

Neuropsychiatric symptoms, such as depression and anxiety are more frequent in women than men. Various factors, such as genetic predisposition, psychosocial vulnerability, excessive stress and somatic diseases may explain gender differences. Moreover a strong association in the precipitation of symptoms seem to be related to the female reproductive cycle: premenstrual tension syndrome, postpartum depression or climacteric depression. These indicated the influence of hormonal fluctuations on the brain. Estrogen modulates several neurotransmitters, has direct effect on neurons by stimulating axonal sprouting, including vasodilatation. These findings lead to the theory that neuropsychiatric symptoms at menopause may be associated with declining estrogen levels and hormone therapy may help in appropriate cases.

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HORMONE THERAPY (HT) AND MOOD

Dementia is a chronic of cognitive abilities and result in prominent changes and personality and ultimately there is deterioration in a person's physical and neurological status. Hence, dementia is a debilitating illness affecting memory and cognition, behavior personality traits level of independence, physical and neurological function. Dementia can be considered as ‘chronic brain failure’ and delirium is associated with reduced attention or consciousness.

Epidemiology

Dementia is a common but not in evitable consequence of aging. Its prevalence and incidence increase with age and risk of developing dementia doubles every 5 years after the age of 65. Approximately 7% of people aged over 65 years are affected, increasing to at least 20% in people aged 80 years and over. It may exceed 50% in those over 90. In 2006, there were 26.6 million sufferers from dementia worldwide. Alzheimer’s disease (AD) is predicted to affect 1 in 85 people globally by 2050 presently it is estimated that 3.7 million Indians aged over 60 years have dementia—2.1 million women and 1.5 million men. Prevalence of dementia is 0.6 to 3.5% in rural India and 0.9 to 4.8% in urban India.

Causes

Dementia is caused by damage to brain cells and different types of dementias are associated with particular type of brain cell damage in particular regions of brain. Dementia is not caused by a single factor. Its presentation can be mixed. It often coexists with other conditions. Generally individual diseases have distinct clinical presentations because they affect specific areas of the brain in different ways. Depending on the underlying pathology, the illness may be reversible, static or most commonly progressive. Alzheimer’s disease accounts for 60 to 80% of cases of dementia. Vascular dementia, which occurs after a stroke, is the second most common that can cause symptoms of dementia, including some, that are reversible, such as thyroid problem and vitamin deficiencies (Table 1).

Symptoms

Symptoms of dementia can vary greatly. At least two of the following core mental functions must be significantly impaired to be considered dementia:

- Memory
- Communication and language
- Ability to focus and pay attention
- Reasoning and judgment
- Activities of daily living
- Visual perception.

Many dementias are progressive if a person is experiencing memory difficulties or other changes in thinking skills, this should not be ignored. Professional neuropsychological, tests aided by brain scans, may detect a treatable condition.

Even if symptoms of dementia are seen, early diagnosis allows a person to get the maximum benefit from available treatments and provides an opportunity to plan for the future.
IMPACT OF DEMENTIA

The average life expectancy of a person with dementia is 3 to 7 years after the diagnosis is made, although diagnosis often occurs some years after first onset of symptoms. It is the fourth most common cause of death.

After heart disease, cancer and stroke. The World Health Organization (WHO) recognizes dementia as one of the major causes of disability worldwide. It causes significant distress to patient, their caregivers and families and has an enormous impact on society.3 Most people with demand live in the community and require a range of supportive services and in the long-term they are likely to require residential or nursing home care.

It is important to stress that although cognitive impairment is a central feature of dementia, psychological and behavioral changes are also common and important symptoms. These frequently cause caregiver stress and are major factors leading to hospital admission and/or institutional care. Women have a central role in providing care and support to people with dementia, either as a member of a family or as a voluntary or aid caregiver.

Table 1: Causes of dementia

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>Alzheimer’s dementia with Lewy bodies, frontotemporal dementia, multiple-system atrophy</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cerebrovascular disease,* hypoperfusion (e.g. after cardiac arrest or septicemia),* chronic subdural hematoma,* rare: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), vasculitis*</td>
</tr>
<tr>
<td>Alcohol/toxic/drug</td>
<td>Alcohol-related,* includes alcohol-related Dementia</td>
</tr>
<tr>
<td>Infective and prior disorders</td>
<td>Prior disorders (e.g. Creutzfeldt-Jakob disease) syphilis,* encephalitis,* HIV-related*</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Head injuries</td>
</tr>
<tr>
<td>Metabolic endocrine and disorders</td>
<td>Hypo/hyperthyroid disease,* Wilson’s disease*</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Vitamin deficiencies (vitamin B12, folic acid, thiamine)</td>
</tr>
<tr>
<td>Genetic</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Primary* or secondary central nervous system</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Tumors</td>
</tr>
<tr>
<td>Demyelinating disorders</td>
<td>Normal pressure hydrocephalus*</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis (as a late complication)</td>
</tr>
</tbody>
</table>

*Treating the underlying cause can potentially modify the course

Effect an patient: It includes distress and symptoms of illness, changes within the home/family, increased dependency on others, decreased independence (e.g. driving), move into institutional care (financial implications), complications of treatments used for symptom, management (e.g. falls, fractures, hyperprolactinemia, osteoporosis cerebrovascular disease), etc.

Caregivers: Imposes significant burden, risk to mental health (particularly, depression) and physical health (e.g. due to physical intervention, such as lifting /moving), as a caregiver, social isolation, fear/uncertainly, loneliness-loss of intimacy/reciprocity, grieving, stigmatization, disruption of family life, decreases quality of life, financial loss, etc.

ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is a major cause of progressive dementia. Alzheimer’s disease is associated with cerebral atrophy most market in the frontotemporal association cortices. Microscopically, it typically shows neurofibrillary tangles and extracellular plaques of beta amyloid proteins. In AD, Tau protein gets hyperphosphorylated creating neurofibrillary tangles and disintegrating neuron’s transport system. Beta amyloid is a fragment of amyloid precursor protein (APP) which is critical to neuronal growth, survival and post injury repair. This leads to degeneration of the cholinergic neurons resulting in deficiency of acetylcholine which has a role in cognition. Scientists consider the time between initial brain change of AD and symptoms of advanced AD to represent the ‘continuum’ of AD.

Prevalence

Alzheimer’s disease is the fourth leading cause of death in asia-pacific region. For India, dementia mortality rate is 13.5 per 100000 males and 11.1 per 100000 females. Mean life expectancy following diagnosis is approximately 7 years. Other coincident diseases, such as heart problems, diabetes, alcohol abuse, are also related. With shortened survival in aging demographics and memory study (ADAMS). A cohort study of individuals born before 1954 in USA. Prevalence of AD was 71.5% in women and 28.5% in men.

Risk Factors

- **Age:** Approximately 1 in 20 people over the age of 65 will develop AD.
- **Gender:** Women appear to be at high risk for AD than men.
- **Are men OR, confidence interval (CI), 1.16 to 2.10**
- **Family history:** risk of developing AD at an earlier age is higher
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if a primary relative is affected:

• Genetic factor; apolipoprotein-E (ApoE), type-4 minimal cognitive impairment (MCI)
• Cardiovascular disease risk factors; physical inactivity, diabetes hypertension, dyslipidemia smoking, obesity
• Autoimmune diseases, depression and stress, head trauma and traumatic brain injury
• Down’s syndrome.

Factors ameliorating dementia are diet, exercise, antioxidants, anti-inflammatory agents and stress reduction.

Diagnosis

Clinically, AD presents as progressive memory loss accompanied by major changes in mood and in the ability to perform common activities. Depression can masquerade as dementia and dementia as depression, commonly they coexist. Alzheimer’s disease is usually diagnosed clinically from patient’s history, collateral history from relatives and clinical observation based on the presence of characteristic neurological and neuropsychological features and absence of alternative conditions.

Characteristically, a person experiences a gradual decline in cognitive function, with core changes summarized as:

• Amnesia (memory)
• Apraxia (action)
• Agnosia (recognition)
• Aphasia (spoken language)
• Alexia (reading)
• Agraphia (writing).

They have the sensitivity of between 94 and 100%. Women suspected to have AD should get thyroid function tests, B12 level, syphilis and HIV tests, kidney function tests, electrolyte levels, test for diabetes, levels of heavy metals, (e.g. lead acalculia (calculation). Based on the National Institute of Neurological and Communicative Disorders (NINCDS) and Alzheimer’s Disease and Related Disorders Association (ADRDA) criteria updated in 2007 AD may be diagnosed by the following criteria:

• Criteria for probable AD
• Dementia of insidious on set
• Progression of symptoms
• No disturbance of consciousness
• Absence of other systemic or brain diseases that produce cognitive and behavioral change
• Criteria for possible AD
• Symptoms consistent with AD
• Variations in presentation of clinical course
• Presence of other systemic or brain diseases that produce cognitive and behavioral change but is not the cause of dementia

• Criteria for definite AD
• Clinical criteria met
• Neuropathological evidence by biopsy or autopsy.

A good history, neurological examination, at mental state screening, backed by tests that evaluate behavior and thinking abilities should be performed. Computed tomography (CT) scan magnetic resonance imaging (MRI), single photon emission computed tomography (SPEN) position emission tomography (PET) can help exclude other cerebral pathology in subtypes of dementia. For early diagnosis of AD two categories of biomarkers can be useful. (1) Biomarkers showing level of beta amyloid accumulation in brain. (2) Biomarkers showing that never cells in brain are injured or actually degenerated. Recent objective marker is examination of cerebrospinal fluid (CSF) for amyloid beta or tau protein and phosphorylated tau protein conc, mercury) tests done. Genetic tests for APOE-4 and other rare genes are available, but they are not routinely advocated.

Management

Psychosocial Measures, Behavioral Therapy and Pharmacotherapy

Major drugs used in AD are as follows:

• Cholinesterase inhibitors: Donepezil hydrochloride, rivastigmine, galantamine
• N-methyl-D-aspartate receptors antagonists: Memantine.

Group 1: Prevent enzyme acetylcholinesterase from breaking down acetylcholine in brain. Increased concentration of acetylcholine leads to increased communication between never cells. It can cause temporary improvement or stabilize AD.

Group 2: Memantine blocks a messenger chemical glutamate. Glutamate is released in excessive amounts when brain cells are damaged by AD causing further cell damage.

Caregiver Care

Diagnosis of dementia sets in motion profound life changes that effect self-esteem, autonomy, interpersonal relationships, employment income, medical care, residential decision and future plans. Patients with dementia require with daily living and eventually long-term supportive care. The caregivers also need help and support.

MENOPAUSE, HORMONE THERAPY AND ALZHEIMER’S DISEASE

Dementia is viewed as end stage disease and it must be distinguished from age-related cognitive decline.
Overall women are at extreme risk compared with men for depression and AD but not for neurovascular dementia. Common place symptoms that accompany the menopause transition namely hot flushes, sleep disturbances and instability suggest that parts of the brain sub serving function other than solely reproductive, are critically impacted by the presence or absence of sex steroids. Estrogen modulate synaptic density neuronal and glial viability and neurotransmitter systems that underpass cognitive, emotional and motor function. It increases the cerebral blood flow and has an antioxidant and anti-inflammatory effect.

Estrogen therapy is not currently recommended for reducing risk of dementia developing in postmenopausal women or retarding the progress of diagnosed AD. Although limited data suggests that early use of hormone therapy (HT) in the menopause may be associated with diminished risk of later dementia. Women's health initiative memory study (WHIMS) trial of estrogen and a progestin and estrogen alone, were two large randomized controlled trials (RCT) conducted in older menopausal women. These studies showed no benefit and potential harm in administering HT to older postmenopausal women. Risk of cognitive decline was particularly increased over the age of 65 years and adverse effect of conjugated equine estrogens (CEEs) were more pronounced in women with lower cognitive function at baseline and among women receiving MPP + E compared to those receiving E alone.

In WHIMS after exclusion of women with baseline impairment hazard ratios (HR) was 1.77 (95% CI, 0.74–4.23, p = 0.20). In E alone trial and 2.1 (95% CI, 1.25–3.84; p = 0.006) in pooled in trials. In estrogen alone trial, mild cognitive impairment was diagnosed in 76 participants in CEE group and 58 in placebo group [HR, 1.34 (95% CI, 0.95–1.89)]. In E + P group HR was similar according to WHIMS, there may exist a critical window for neuroprotection. Henderson et al, in 2007, reanalyzed the data from WHIMS. All cause dementia was significantly less likely to develop in women reporting prior HT. In 106 pooled cases adjusted HR was 0.54 (95% CI, 0.16–0.85), for those with non-alzheimer dementia HR was 0.75 (95% CI, 0.36–1.39). Case control studies of women who underwent oophorectomy before menopause, have recently shown small risk of dementia and parkinsonism 813 women who underwent unilateral oophorectomy and 676 who underwent bilateral oophorectomy before onset of menopause compared with 1,472 referent women, HR for cognitive impairment was 1.46 (95/CI, 1.13–1.90) adjusted for education type of interview and history of dementia. Women experiencing verbal memory changes at menopause can be advised there is no apparent association between verbal memory change and global cognitive decline. Very few clinical trial support use of estrogen therapy (ET) for cognitive benefits, when initiated immediately after surgical menopause. To date clinical trials of ET have demonstrated no substantial effect of episode memory or executive functioning. Natural menopause has a significant but small effect on some aspects of cognitive that may be time limited. This effect is not explained by menopausal symptoms. In study of women's health across the nation who initiated HT/ oral contraceptives (OC) before their final menstrual and then discontinued had a beneficial effect whereas women who initiated hormones after final menstrual period had diminished effect on cognitive function. The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year ET use and 23 per 10,000 per year of estrogen-progestin therapy (EPT) use.

Cache county study showed that there is reduction in AD risk in HT users who initiated treatment within 5 years after menopause. This reduction was greater with sustained use of 10 years or more keeping in line with the theory of window of opportunity.

Nonoral route of delivery of estradiol that approximate 100 pg/ml or lower may minimize risk of vascular compromise and stork while enchasing synaptogenesis, neural metabolism, and neurotransmission and brain plasticity, conferring neurotransmission. Cognitive preservation was more strongly associated with bioavailable estradiol, estrogen receptor (ER) alpha agonist, than with total estradiol. Selective estrogen receptor modulators (SERMs), aromatase inhibitors or mainly ER beta agonist, like phytoestrogens cannot garner complete protection. By the time dementia tos or mainly ER beta agonists, like phytoestrogens cannot garner complete is clinically evident, there is significant loss of neurons and glia and it is unrealistic to expect HT to revive dead tissue or restore brain architecture.

For best preservation of memory and cognition women should be advised about the importance of good overall health, good cardiac and vascular health, exercise, maintenance of active mind, avoidance of excessive, alcohol consumption measures to reduce risk of diabetes and hypertension. Hormone therapy is not indicated for neuroprotection.

Genetics may be responsible for only a third of AD risk, with the rest dependent on modifiable factors, according to the MacArthur studies of successful aging. There may be a major role for lifestyle medication in preventing AD, exercise, mental stimulation, stress management and nutrition.
Exercise

Of all lifestyle approaches that might contribute to AD prevention, the strongest evidence exercise. Active animals have larger hippocampi, and older people who walk regularly (even as little as 15 minutes a day) have a lower risk for AD. It has been noted that people who routinely exercise exhibit better cognitive abilities and actually have larger brains. Regular exercise also results in lower the biomarker Pittsburgh compound B PIB and A radio labelled glucose analog fluorodeoxyglucose FDDNP [2-(1-6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl ethylidene)malononitrile] binding in the brain indicating the glucose metabolism, reduced CSF tau, and increased CSF amyloid, all markers of decreased AD risk.

MENTAL STIMULATION

Mentally stimulating activities and certain brain—training programs are in the long-term associated with lower brain amyloid levels a decreased risk for AD engage in life-long learning.

Stress Management

Stress is known to effect cognitive function. Sapoisky et al have shown in animal studies that stress is linked with memory impairment and reduced brain size; specifically, glucocorticoids released during stress appear to impair neuronal plasticity and dendrite atrophy, particularly in the hippocampus, stress hormones impair prefrontal cortical functioning, affecting mental affecting mental flexibility and attention. Date indicates that AD, depression and additionaly relaxation, meditation affects biomarkers of inflammation and telomerase activity positively.

NUTRITION

Weight management and nutrition also play major roles in brain health. Several studies support an association between being overweight and increased dementia risk, including recent twin study controlled for sex, education, diabetes, hypertension, stroke, and heart disease. Concurrent work found that cognitive function improved significantly in obese patients who underwent bariatric surgery. Mediterranean diets high in omega-3 fatty acids improved working memory and reduce risk for mild cognitive impairment, minor neurocognitive disorder and AD. Antioxidant-rich fruits and vegetables improve cognition while refined sugars and fats impair it. Areas with turmeric and curry-heavy diets, such as India have lower rate of AD. Another study is looking at pomegranate extract, as daily consumption is associated with improved verbal memory.

REFERENCES