Alzheimer's Disease: Are Women More Susceptible?

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Abstract :

Alzheimer's Disease, is a serious public health problem at old age with increasing societal burden in both developed and developing countries. It is the most common form of Dementia, characterized by loss of memory, cognition and behavioural problems. Interestingly, the disease has been found to affect women in higher frequency with both severity and prevalence. This review work will explain the role of different factors associated with this sex difference in the causation of the disease, specially the role of female sex hormone Estrogen. Several research experiments on large number of post menopausal women have proved beneficial effect of hormone estrogen replacement therapy (HRT) for improvement of cognition and memory. However subsequent experiments have revealed both the benefits and risks of the hormone replacement therapy for the improvement of cognition or control of the Alzheimer's disease. Earlier, Researchers claim more women than men are victims of Alzheimer's disease and dementia, as the former live longer. But nowadays, differences in brain connectivity and sex-specific genes and some other factors are given much importance as the associated links.

Key words: Alzheimer's disease, Estrogen, Hormone Replacement therapy, cognition.

Introduction :

Alzheimers Disease, is not a new disease , but known for more than 100 years ago. Nowadays, it has become a household name and a serious public health problem at old age with increasing societal burden in both developed and developing countries though it is still one of the most misunderstood, under reported diseases .**(46).** It is the most common form of Dementia , a degenerative disorder of brain characterized by loss of memory, cognition and behavioural problems. **(45).** At present, it is one of the leading causes of death in USA. **(47).**. Researchers have confirmed two hall marks of pathological lesions in this disease, these are deposition of abnormal proteins outside the cells (Beta Amyloid proteins) and with in the cells (Neurofibrillar Tangles) **(45) [Fig 1]** Numerous studies suggest that the disease affects the women community more severely compared to the men **(1,2,3,5).** In USA, statistical report says more than 5.5 million people are suffering from this disease and two third of them are women. The first identification of this disease by Alois Alzheimer though made in a woman in 1906, basic and clinical research always overlooked male-female difference in this pathological area. But the disease indeed affects women in higher frequency with both severity and prevalence. **(12).** Inclusion of women in the clinical research area was approved much later with due consideration of gender related differential outcome of health conditions or effect of medications **(4)**.

No one can deny that cognition declines with ageing and a few studies have disclosed that the decline is more noticeable among women with the level of education being one of the risk factors. **(6,7)**. On the contrary, some other workers reported differently. **(2,3,8)**. For more than three decades, various researchers had noted that the incidence of the disease is greater in women community **(9, 10)** Later, other workers expressed the possibility of lack of female sex hormone Estrogen for development of A.D. Their argument was that experiments on large number of women who had undergone postmenopausal estrogen replacement therapy could reduce the risk for A.D. **(11)**.

In this review, we shall first present a brief overview of the research on this disease stressing on the fact for the loss of cognition at old age with special discussion on the neurobiological and behavioural effects of female sex hormone estrogen which may be significant in the ageing process, along with role of some non hormonal factors. In fact , with the advent of medicine and due care during the event of child birth, life span of women community in the last few decades, has been increased, and has put one third of their life span in the post menopausal state when they have to spend their days without the neurotropic and neuroprotective roles of estrogen as they had enjoyed in their

child bearing age. . The centre of verbal and working memory and its retrieval at hippocampus and frontal lobe contains Estrogen receptors (ERs) and it can be assumed that this hormone has important role in the cognitive functions. Estrogen appears to be important for the regulation and maintenance of network integrity of several brain areas related to cognition (**12**). Considering this, the present review work has been carried out with the inclusion of research studies made in more than the last three decades..

Review of literature:

A. Basic Role of Several factors: It is now well established that Alzheimer's Disease or A.D is a multifactorial disease and a disease of the old age. The said factors are **Age**, **Sex**, **Family history/ Genetic inheritance**, **Educational level** , Sex Hormone, whether **Victims of Hypertension, Diabetes, Obesity, Smoking, Alcohol intake, Head injury and Stress (48)**

B. Role of gender specific Gene(s) : Apart from the age factor and others, gender specificity of the disease have been studied epidemiologically as can be seen in Fig 2,3, and 4. Evidence indicates that genes specific to women and men could be linked to Alzheimer's risk**. (49)** But scientists do not know as yet why certain genes are linked with Alzheimer's risk in one sex and not the other. Apolipoprotein E also known as APOE, is a gene associated with varying risks of AD. Of the three different APOE types (APOE2, APOE3 and APOE4), the APOE4 type is associated with the increased risk for AD. Women with APOE4 are found to be victims of mild cognitive impairment or AD than men with AD **(57, 58)**, worse memory power **(60)**, greater brain atrophy and lower brain metabolism **(59)**. These information thus could provide some answers as to why more women are living with dementia than men.

C. **Lack of Estrogen and cognitive impairment :**

For more than three decades, it has been proved by various researchers that the incidence of the disease is greater in women community . Later other workers expressed the possibility of lack of female sex hormone Estrogen for development of A.D. Their argument was that experiments on large number of women who had undergone postmenopausal estrogen replacement therapy could reduce the risk for A.D. So long, women are in the reproductive years, Estrogens and Progesterone are produced cyclically by the ovaries. .During peri-menopause, there appears fluctuations in the hormonal milieu. Finally, beyond menopause, due to the depletion in ovarian follicles, circulating levels of these sex steroids are permanently reduced. These hormonal changes at the menopausal transition and postmenopause phase, alter neural activities, specially neural processes concerned with cognition and pathological processes linked to Alzheimer's disease. Menopause denotes the end of normal spontaneous ovarian function and reproductive life of the woman**.** Associated endocrine changes accompanying this stage of life involve gradual though erratic decline in the levels of estrogen for several years.**(14).** This condition culminates into drop to a low level in estrogen in the postmenopause **. (15).** These changes in estrogen levels have been speculated to account for the increased reporting of memory complaints during this period. **(16,17).** In this context, experimental evidence indicates that estrogen has neuroprotective and neurotrophic effects **(18)** and, after menopause, brain atrophy in women accelerates at a faster rate than in men. **(19.).** Estradiol has been found to decrease the formation of Aβ (**20**) and reduces tau hyperphosphorylation (**21**)**.** It can also enhance neurogenesis within the dentate gyrus of the hippocampus **(22)**. Moreover, estradiol has proven to facilitate long-term potentiation in the hippocampus (**23**). However, laboratory investigations and some human evidence indicate that effect of the relevant hormone might vary by dose, type of estrogen, type of progestogen, mode of administration, and cyclicity **(24).** The centre of verbal and working memory and its retrieval at hippocampus and frontal lobe contains Estrogen receptors (ERs) and it can be assumed that this hormone has important role in the cognitive functions. Estrogen appears to be important for the regulation and maintenance of network integrity of several brain areas of brain. During normal ageing, it is well established that the gonadal and adrenal steroid hormones regulate vital neuronal and glial functions by different mechanisms (**25**)**.** At this backdrop, researchers tried to determine whether the estrogens administration to perimenopausal or post menopausal women would protect them against devastating decline in cognition that normally occur with increasing age. Their findings highlight the importance of sex steroids in the development and the regulation of the CNS. To add to this information, it is also true that biologically, marked differences exist in the structure and function of the brain of male and female animals and humans **(26)** Also, many of the areas of brain of both animals and humans show gender dimorphism, such as different numbers of cells in specific areas .This kind of different organization of brain areas in males and females seems to be due to the action of sex steroid hormones as demonstrated by the differential expression of steroid receptors in sexually dimorphic nuclei **(27)** Moreover, estrogen

has the control over the anatomy and connectivity of the hippocampus and associated structures **(28, 29)** During peri menopausal and post menopausal period, due to lesser production or failure of production of gonadal hormone, neurotransmitters, neuropeptides and neurosteroids undergo important changes and many of the CNS activities deteriorate, particularly those associated with hippocampal *functions* such as memory, attention, cognition and autonomic control **(30.).**

Receptors of estrogen are also found in other areas of CNS, such as amygdala, cortex basal forebrain, cerebellum locus coeruleus midbrain rafe nuclei, glial cells and central grey matter, confirming an involvement of estrogen in controlling well-being, cognitive functions and memory processes in physiological as well as in pathological conditions **(31).** Although it remains under debate **(32)**, positive correlations between endogenous estrogen levels and cognitive function have been reported **(33, 34)**

D. Role of Estrogen containing HRT in management of Alzheimers Disease.

Basic science usually proclaims that estrogen therapy may promote neurological health and may ameliorate Alzheimer's disease. At first, use of hormone therapy among women with Alzheimers disease was found to be associated with better cognitive skills**.(35)**. In earlier days, small uncontrolled and nonrandomized studies raised some hope that use of an estrogen or an estrogen plus a progestogen would improve cognition status in this disorder **(36)**. Various studies suggest that estrogen treatment has positive effects on memory and cognition when it is administered to naturally menopausal women shortly after the cessation of their menstrual cycles or immediately following surgical menopause. On the contrary, later clinical and epidemiological data showed the reverse picture, i.e. hormone replacement therapy (HRT) did not offer any benefit , even a potential deleterious effect. Estrogen treatment to older women offer a little beneficial or even detrimental effects on cognitive ageing. Naturally, a question came up, about the role of estrogen in HRT. In fact, role of two major determining factors appeared, i.e. the time at which estrogen therapy is initiated, the neurological status of the brain at the time of estrogen therapy initiation and the type of progestogen used in HRT , and to sustaining neurological health and function. A hypothesis is thus put forth that proclaims for both the benefits and risks of estrogen therapy. **(37)**. Previously, the Women's Health Initiative Memory Study (WHIMS) reported that effect of estrogen and progestin on global cognitive function in postmenopausal women aged 65 years or older did not improve cognitive function when compared with placebo. **(38)**. The effect of estrogen-alone therapy, when evaluated in WHIMS, revealed that for women aged 65 years or above, estrogen therapy had an adverse effect on cognition, and this was greater among women with lower cognitive function at initiation of treatment **(39).** Human research described above, however, thus far fails to demonstrate convincing roles for these compounds in Alzheimer treatment or prevention, but the uncertainty in the outcome of the research studies through human experiments indicate that the effects of relevant hormone might vary by dose, type of estrogen, type of progestogen, mode of administration, and cyclicity **(40,41).**

E, Other factors:

1. **Role of Physical Exercise**: Research studies reveal that People who exercise**,** are less likely to develop dementia, particularly Alzheimer's disease **(53)**. This has been corroborated by a recent observational study which reported that women who possessed high fitness level were 88% less likely to develop dementia compared to those who were at medium fitness level **(54)**. However, in spite of reported benefits of exercise, women do not usually practice exercise and if at all, do, they exercise less than men, which is only partly accounted for by gender differences in parenting roles. **(49)**. Interestingly, The magnitude of the benefit from exercise appears to vary in women depending on estrogen levels, with greater benefits observed when estrogen levels are high. **(55).**

2. **Burden of Care giving**: Women make up about 60% of all family caregivers for Alzheimer's patients. Women caregivers also have a two-fold higher caregiver burden than male caregivers and are more likely to leave their job to care for a family member. Some studies suggest that spousal caregivers may be at a higher risk of cognitive impairment or dementia than non-caregivers. **(56).**

3. **Role of Depression** : Depression is an important factor for higher dementia risk **(50)** and women are two-fold more susceptible to depression than men **(51).** Additionally, persons suffering from depression revealed a smaller hippocampus, in women, but this association was not observed in men. **(52)**. A history of depression is also associated with faster shrinkage of the hippocampus in women but not in men. The reasons for these sex differences, however, are currently unknown.

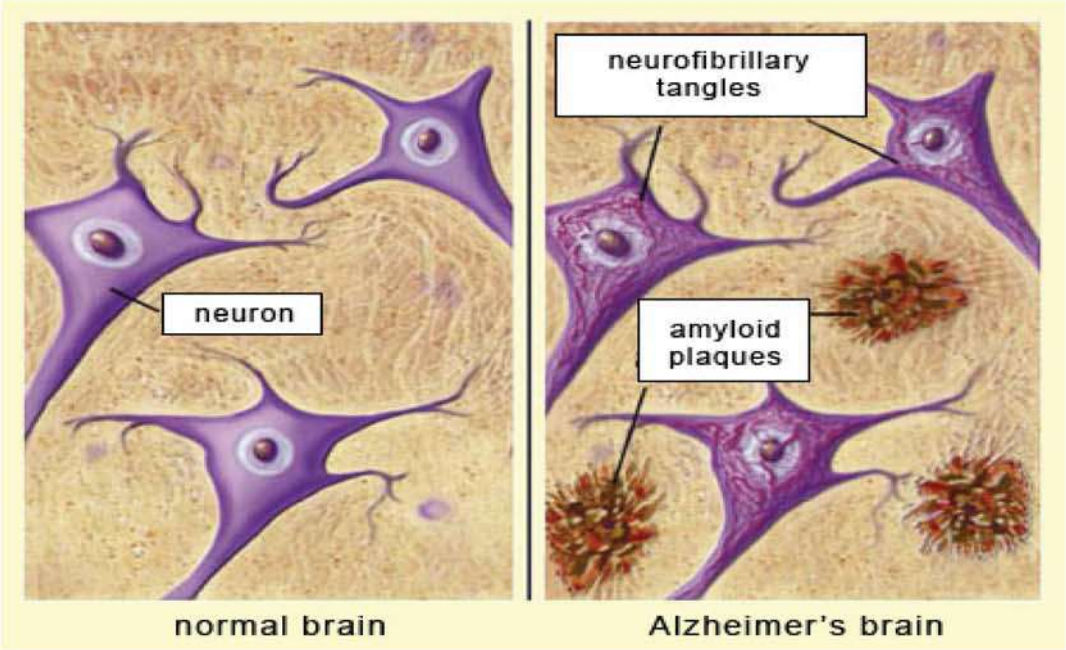

Fig 1

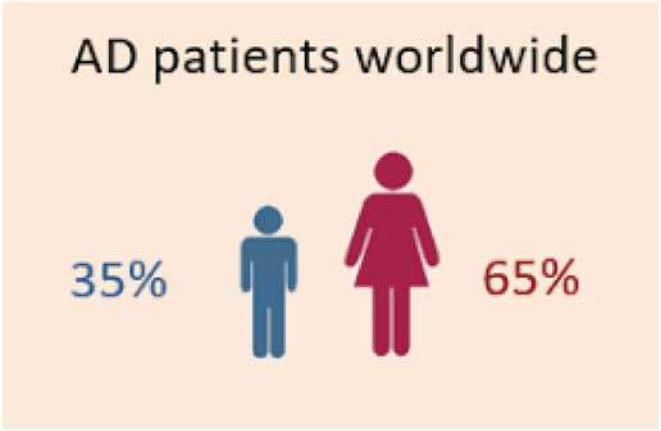

Fig 2

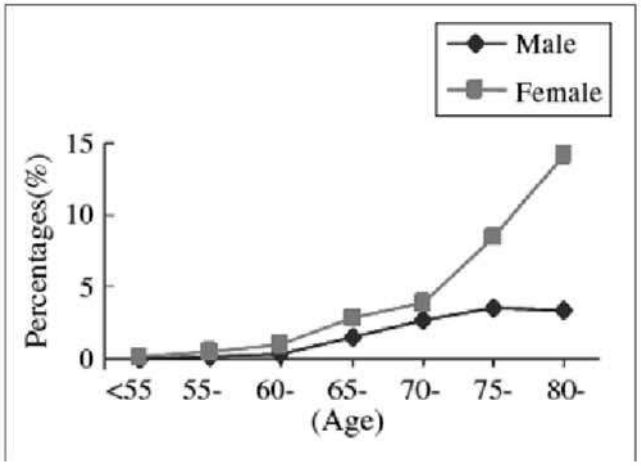

Fig 3. Alzheimers Disease: Gender Difference
Ref: World data for 2009.

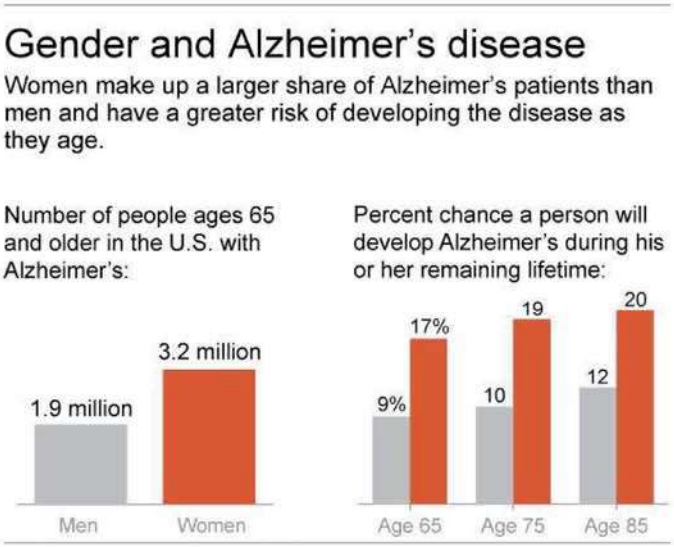

Fig 4. . Alzheimer's Data 2018

Conclusions: Alzheimer's Disease disproportionately affects women in both prevalence and severity**.** But the biological mechanisms underlying these sex differences are not yet fully understood**.** From the extensive literature survey, it appears that the variability of HRT effects across cognitive domains and in relation to age and timing of initiation has yet to be carefully studied. Therefore, a 'critical period' shortly after menopause, when HRT needs to be prescribed to protect cognitive function, has been suggested, but definitive data to demonstrate it are yet to achieve. In addition, whether this critical period is related to decreased responsivity of neurons to estrogen with increasing age or to the inability of the hormone to reverse brain dysfunction which may have occurred during the time between menopause and the initiation of treatment ≥ 10 years is not known. Menopausal Hormone Therapy (MHT) when applied to postmenopausal women with mild cognitive impairment (MCI) for a long time using percutaneous estrogen gel and oral MP4, showed attenuation in cognitive decline. **(42)**.

But the picture is not always so bright. **(43)**. Another study on the Finnish post- menopausal case-control hormone therapy (HT) and Alzheimer's disease revealed use of both systemic combined and oestrogen only (estradiol) HT to be associated with a 9 to17% increased risk of Alzheimer's disease.. The result of the study compelled the authors to think that HT users should be informed of the risk of Alzheimer's disease with prolonged use. **(44)**. Role of genetic factors, life style factors in case of women , such as exercise, mental stress , depression etc in modern days are gaining some importance for the explanation of the gender dominance of the disease. Therefore, more research is needed to understand specifically how AD differs between men and women., specially in the areas of sex differences in brain development and brain aging, and sex differences in detection, diagnosis and treatment of AD.

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