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Review Article

Sympathovagal Imbalance and Cognitive Deficit in Postmenopausal Women: A Mini Review

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ABSTRACT
Menopause is a Greek word meaning, 'meno' – month, 'pause'–ceases. Menopausal transition includes autonomic dysfunctions like somatic symptoms, vasomotor symptoms and mental disturbances such as mood changes, depression, irritability, forgetfulness and lack of concentration that decreases the quality of life. These climacteric vasomotor symptoms are due to alteration of autonomic hemodynamic regulation. Recently, there developed a concept of increased cardiovascular risk and mortality in individuals with sympathovagal imbalance. Sympathovagal imbalance has been observed in postmenopausal women. Cardiovascular risk has been shown to be associated with cognitive decline in elderly postmenopausal women. Sympathovagal imbalance with increased sympathetic and decreased parasympathetic activity could be linked to cognitive decline after menopause in women.
Key words: Postmenopausal women, Heart Rate Variability, Cardiac Autonomic Functions, Cognition, Sympathovagal imbalance.

INTRODUCTION

Menopause refers to a point in time that follows one year after the cessation of menstruation.[1] Menopause is a Greek word meaning, 'meno' – month, 'pause' – ceases.[2] It is a gradual transition from the reproductive to the post-reproductive stage of women's life.[3] According to the third consensus meeting of Indian Menopause Society (2008), India has a large population, which has already crossed billion mark, the number of menopausal women about 43 million. It has been projected that in 2026 the population in India will be 1.4 billion, the menopausal population will be 103 million.[4] In Indian women the mean age of menopause is 47.5 years.[4]

Menopausal transition includes autonomic dysfunctions like somatic symptoms, vasomotor symptoms, sexual dysfunctions, urological symptoms, psychological and mental disturbances such as mood changes, insomnia, depression, irritability, forgetfulness and lack of concentration that decreases the quality of life.[1,5] It was reported that the prevalence of any one of the post-menopausal symptoms was 88.1% and the most common was vasomotor symptoms (combined hot flushes and night sweats). These climacteric vasomotor symptoms are due to alteration of autonomic hemodynamic regulation like various cardiovascular reflexes and dysregulation of cutaneous blood flow.[6]

In Indian women the incidence of Cardiovascular Disease (CVD) is significantly rising. The projected deaths from cardiovascular diseases were estimated to be 42% of the total deaths by the year 2020.[4] Premature, surgically induced menopause has been shown to increase the risk for CVD.[7] CVD has been shown to be associated with cognitive decline in elderly postmenopausal women.[8] For the past two decades, there developed a concept of increased cardiovascular risk and mortality in individuals with Sympathovagal Imbalance (SVI) like increased sympathetic activity and reduced parasympathetic activity.[1] SVI is observed in postmenopausal women.[9] Large RCTs in older women showed decrease in cognitive function.[4] Thus, SVI and decline in cognitive function are present in postmenopausal women.

Sympathovagal Imbalance

Autonomic Nervous System (ANS) have two major divisions: sympathetic and parasympathetic, where the former helps in energy expenditure and the later helps in energy storage.[10] Both these divisions act in a reciprocal manner, that is, if one is stimulated the other one gets inhibited and vice versa.[11] Sympathovagal balance is the balance between the sympathetic and parasympathetic activity of the individual at any given point of time.[12] Increased or decreased activity of any of the divisions of ANS results in SVI. ANS is also influenced by estrogen in postmenopausal women.[6] Recently it has been identified that the estrogen receptors are also present in heart, vascular smooth muscle and Nucleus Tractus Solitarius (NTS) that regulates the autonomic nervous system.[13] In female subjects, though age has an important role in cardiac autonomic regulation, this age related alterations are reduced by estrogen therapy, by promoting decreasing the

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sympathetic hyperactivity of heart.[14] Power spectral analysis of Heart Rate Variability (HRV)[11] and Conventional Autonomic Function Test (CAFT),[15] have been documented as sensitive measures of sympathovagal balance. Parasympathetic dominance is favourable, whereas defective vagal tone is deleterious and increases the risk of cardiovascular diseases.[16] This altered sympathovagal balance imparts an undesirable effect on health.[17] Sympathovagal Imbalance (SVI) is a better predictor of cardiovascular risk.[10]

Heart Rate Variability

Heart Rate Variability (HRV) was first identified by Hon and Lee, who appreciated a fluctuation in RR interval which antecedes fetal distress, in the year 1965.[10] HRV mainly concentrates on the fluctuations in the RR interval between the successive heart rates.[18] HRV analysis is an inexpensive, non-invasive and quantitative tool to assess the sympathovagal imbalance.[11,19,20] One of the most sensitive tool to assess sympathovagal imbalance is by performing power spectral analysis of HRV which assesses both the amount and nature of dysregulation in the autonomic control over heart by time domain and frequency domain parameters.[11,19-21] Both sympathetic and parasympathetic system has an influence on heart rate and its variability with parasympathetic overhand.[20] Reduced HRV is associated with various cardiovascular risk and increased risk of mortality.[20] Among all the time domain parameters RMSSD and SDNN have high sensitivity.[20] Short term vagal control of heart rate is solely demonstrated by changes in RMSSD. In a recent study, diabetics were found to have decreased RMSSD.[20] SDNN, which is the standard deviation of normal to normal intervals in milliseconds indicates the vagal tone over heart.[19] LF/HF ratio is a marker of sympathovagal imbalance. One of the best indicator of diminished cardiac function is heart rate variability.[22]

Measurement of HRV

HRV is measured by three methods

- Time domain methods
  - SDNN
  - RMSSD
  - NN50
  - pNN50
  - HRV triangular index
  - Triangular interpolation of NN (TINN)
- Frequency domain methods
  - Very Low Frequency (VLF)≤0.04Hz
  - Low Frequency (LF) - represents the sympathetic modulation – 0.04-0.15 Hz (9,12)and in particular of the RR period (heart rate variability, HRV.
  - High Frequency (HF) – represents the parasympathetic modulation – 0.15-0.4 Hz (9,12)and in particular of the RR period (heart rate variability, HRV.
  - Total Power (TP) - ≤ 0.4Hz
  - LF nu – LF/ (Total power-VLF) × 100
  - HF nu – HF/ (Total power-VLF) × 100
  - LF/HF – Ratio of balance of sympathetic and parasympathetic arm of the ANS.[18,11]

Heart Rate Variability and Menopause

Immediately after menopause there occurs a decline in heart rate variability. Though the decline in estrogen level occurs after six months of the last menstrual period, the decrease in HRV can be demonstrated only after a year of Last Menstrual Period (LMP).[22] LF nu was significantly increased in women taking hormone replacement therapy.[13] Increased high frequency component among young women may be responsible for decreased risk of cardiovascular diseases compared to men of same age.[20]

SDNN and RMSSD, believed to be expression of vagal tone were reduced in postmenopausal women.[18] Estrogen therapy increases HRV in postmenopausal group and addition of progestin in hormone replacement therapy was found to decrease HRV in a recent study.[20] HRV was also found to be altered in early postmenopausal women with increased Low frequency, decreased high frequency component and decreased LF/HF ratio.[9]

Cardiac Autonomic Function Test (CAFT)

The cardiac autonomic functions tests involve the following

30:15 ratio – assessed by lying to standing test (heart rate and BP response from lying to standing).

- HR response and BP response to standing evaluates the parasympathetic branch and sympathetic branch of autonomic nervous system respectively.[23]

E: I ratio – assessed by deep breathing test (Heart rate response to deep breathing exercise).

- Heart rate *response* to deep breathing test is a non-invasive, most sensitive and specific, reproducible marker for vagal function over heart.[24]

ΔDBP_{IHG} – Isometric handgrip exercise test (blood pressure response to sustained isometric hand grip).

- Isometric Hand Grip (IHG) test is a simple, sensitive, specific, non-invasive and reproducible test for assessing sympathetic function.[25]

CAFT and Menopause

Studies demonstrated that in postmenopausal women there occured a decrease in both sympathetic and parasympathetic reactivity.[6] Surgical menopause increased sympathetic reactivity and reduced vagal tone.[6] E: I ratio and 30:15 ratio, which assess the parasympathetic function were significantly low in postmenopausal compared to premenopausal women.[13,17] Autonomic function tests also vary during menstrual cycle. E: I and 30:15 ratio were significantly higher in secretory phase compared to proliferative phase of menstrual cycle, which is due to parasympathetic dominance in secretory and increased sympathetic activity in proliferative phase.[13] E: I ratio and 30:15 ratio were significantly low in postmenopausal women on hormone replacement therapy compared to postmenopausal women without hormone replacement therapy.[13] The sympathetic function test like orthostatic tolerance test, cold pressor test, sustained isometric handgrip exercise test (DBP), was also found to be increased in postmenopausal group.[17] Study has shown an increased sympathetic tone in postmenopausal women.[13] In contrast, the deep breathing test and Valsalva maneuver test did not show any significant difference in the postmenopausal group compared to the premenopausal group.[18] There is shift of autonomic balance to the side of sympathetic system after menopause, which is attributed to decreased estrogen production.[17]

Cognition

Cognition is evoked response to stored stimuli. It is a thinking process of brain, using both the sensory input and memory.[26] Cognitive process involves various neurotransmitters and involves signals originating in different regions of brain.[26] Other than ageing there are other pathological factors that also cause a decline in cognition, which includes socioeconomic status, vascular disease like hypertension, diabetes mellitus,

dyslipidemia, altered fibrinogen levels and adverse lifestyle habits.[27] The incidence and prevalence of dementia and Alzheimer's disease is increasing tremendously. So it is a promising task to diagnose memory impairment at the earliest to treat the condition. Event related brain potentials, such as P300, Mini Mental Status Exam (MMSE) and Wechsler Memory Scale (WMS-III) are the various tools to assess the cognitive functions.[28] Recent study shows a reduction in amplitude and increase in latency of P300 wave with ageing, in dementia patients and in patients with various neurological problems[29] like schizophrenia, major depression.[30] As in the year 2003, the ratio of number of people more than 60 years was found to be 1 in 10 and the projected figure in the year 2050 will increase to 1 in 6.[29] Not only ageing but also menopause which is an inevitable event in a women life also causes a decline in cognition.[28]

Cognition and Menopause

Study shows a reduction in amplitude and increase in latency of P300 wave in menopausal women.[28] Perimenopausal women show atrophy of different regions of brain that are involved in memory like hippocampus and parietal lobe and it has been related to the decreased estrogen level during this period.[26] One of the target organs of estrogen is brain. Some specific regions of brain express estrogen receptors.[31] Estrogen is found to have influence on the neuronal growth and its plasticity, hippocampal neurogenesis and long-term potentiation responsible for episodic memories.[28,31] Estrogen protects against apoptosis and neural injury by excitatory neurotransmitters, β-amyloid, oxidative stress and ischemia. Estrogen has an influence on many neurotransmitter systems like acetylcholine, serotonin, noradrenalin and glutamate. Cholinergic neurons releasing acetylcholine has a very important role in the process of memory and neurons in the basal forebrain express estrogen receptors and estrogen supplementation after ovariectomy increases cholinergic function.[31] Functional brain imaging studies demonstrate that estrogen modulates neural activity during performance of cognitive tasks. Around the time of the menopausal transition, many women report problems with memory, perhaps suggesting that hormonal changes associated with menopause are linked to memory complaints. In contrast to the natural menopausal transition, estrogen could impact memory when ovarian estrogen production is abruptly curtailed.[31] Estrogen Therapy (ET) /Hormonal Therapy (HT) seems to reduce the risk and delay the onset of Alzheimer's disease and seems to increase verbal memory and attention in younger postmenopausal women[4] Hormone replacement therapy is found to decrease the latency and increase the amplitude of P300 wave in postmenopausal women with dementia.[28] In contrast, estrogen replacement therapy in some studies have led to cognitive decline or no association with cognitive performance.[26]

Association of Sympathovagal Imbalance with Cognition

There is shift of autonomic balance to the side of sympathetic system after menopause, which is attributed to decreased estrogen production.[18] Menopause is associated with cognitive change.[4] Children with increased resting heart rate variability demonstrated better working memory and reduced reaction times.[32] Low frequency was negatively correlated with various cognitive domains like memory, phonemic, semantic fluency and the Mill Hill Vocabulary Test.[33] In subjects with Alzheimer's disease and mild cognitive impairment, reduced HRV was found to be correlated with cognitive deterioration.[34] Studies have also demonstrated that reduced high frequency of HRV was associated with increased risk of cognitive impairment.[35] Cholinergic system has an important role in cognitive processing and its dysfunction is found to impair various domains of cognition.[28] Thus cognitive changes in menopausal women could be linked to autonomic dysfunction.

CONCLUSION

Sympathovagal imbalance is reported to be associated with cardiovascular risk and cardiovascular disease is associated with decline in cognitive function in postmenopausal women. There is increased risk of cognitive decline in postmenopausal women compared to women in reproductive phase. Sympathovagal imbalance with increased sympathetic and decreased parasympathetic activity could be linked to cognitive decline after menopause in women. As yoga has been shown to improve sympathovagal balance, further study should be conducted to explore the possibility of improving cognitive functions in postmenopausal women by lifestyle intervention such as yoga.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

SVI: Sympathovagal Imbalance; **CVD:** Cardiovascular Disease; **ANS:** Autonomic Nervous System; **HRV:** Heart Rate Variability; **CAFT:** Cardiac Autonomic Function Test.

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