COGNITIVE DISORDERS IN PREMATURE MENOPAUSE

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Abstract

Premature menopause, or premature ovarian insufficiency, affects 1% of women under the age of 40. Beyond the crucial role of estrogens in the reproductive ability of the woman, there are also many other, and equally important, factors - such as cognitive function. The causes that lead to premature menopause have not been precisely determined.

A literature search was conducted on cognitive disorders in menopausal women and animal models, focusing mainly on premature menopause.

Most women in menopause (around 70%) report a deterioration of their memory acumen in the peri-menopausal period. Cognitive decline precipitates as a direct consequence of the decrease in estradiol. Estrogens, besides their effect on neurotransmitter levels and activity, also promote neuronal growth and synaptogenesis by acting as antioxidants and regulating the homeostasis of calcium and the secondary messenger systems. The deterioration of the cardiovascular function, which often accompanies the peri-menopausal period, maybe a route through which cognitive functions are driven to deterioration when in premature menopause since vascular risk factors have been known to correlate with cognitive deficits and dementia.

Premature menopause affects the central nervous system leading to cognitive impairment or even dementia, mainly due to the decreasing estrogen level and comorbidity with cardiovascular risk factors, autoimmune diseases, and aging.

Key-words: premature menopause, premature ovarian insufficiency, cognitive disorders, cognition, cognitive function

ΝΟΗΤΙΚΕΣ ΔΙΑΤΑΡΑΧΕΣ ΣΤΗΝ ΠΡΟΩΡΗ ΕΜΜΗΝΟΠΑΥΣΗ

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Περίληψη

Η πρόωρη εμμηνόπαυση, ή πρόωρη ωοθηκική ανεπάρκεια, επηρεάζει το 1% των γυναικών κάτω των 40 ετών. Πέρα από τον κρίσιμο ρόλο των οιστρογόνων στην αναπαραγωγική ικανότητα της γυναίκας υπάρχουν και πολλές άλλες επιδράσεις τους, εξίσου σημαντικές, όπως στη γνωστική λειτουργία. Τα αίτια που οδηγούν σε πρόωρη εμμηνόπαυση δεν έχουν προσδιοριστεί με ακρίβεια.

Διεξήχθη βιβλιογραφική έρευνα για τις γνωστικές διαταραχές στις εμμηνοπαυσιακές γυναίκες και σε αντίστοιχα πειραματικά μοντέλα, εστιάζοντας περισσότερο στην πρόωρη εμμηνόπαυση.

Οι περισσότερες γυναίκες στην εμμηνόπαυση (περίπου το 70%) αναφέρουν επιδείνωση της μνήμης τους στην περιεμμηνοπαυσιακή περίοδο. Η γνωστική έκπτωση προκύπτει ως άμεση συνέπεια της μείωσης της οιστραδιόλης. Τα οιστρογόνα, εκτός από την επίδρασή τους στα επίπεδα και τη δραστηριότητα των νευροδιαβιβαστών, προάγουν την ανάπτυξη των νευρώνων και το σχηματισμό συνάψεων, δρώντας ως αντιοξειδωτικά και ρυθμίζοντας την ομοιόσταση του ασβεστίου και του συστήματος των δεύτερων αγγελιοφόρων. Η επιδείνωση των καρδιαγγειακών παραγόντων κινδύνου που συνοδεύουν την περιεμμηνοπαυσιακή περίοδο πιθανόν είναι μια επιπλέον οδός μέσω της οποίας οι γνωστικές λειτουργίες επιδεινώνονται με την πρόωρη εμμηνόπαυση, καθώς οι αγγειακοί παράγοντες κινδύνου έχουν αναφερθεί ότι σχετίζονται με γνωστικά ελλείμματα και άνοια.

Η πρόωρη εμμηνόπαυση επηρεάζει το κεντρικό νευρικό σύστημα οδηγώντας σε γνωστική έκπτωση ή ακόμα και άνοια, κυρίως λόγω της μείωσης των επιπέδων οιστρογόνων και της συννοσηρότητας με παράγοντες καρδιαγγειακού κινδύνου, αυτοάνοσα νοσήματα και γήρανση.

Λέξεις-κλειδιά: πρόωρη εμμηνόπαυση, πρόωρη ωοθηκική ανεπάρκεια, νοητικές διαταραχές, νόηση, νοητική λειτουργία

Introduction & methods

Menopause usually occurs at around age 50, but in some cases, it can trigger between the 41st and 45th year of age (early menopause) or even at age 40 (premature menopause). Premature menopause, or premature ovarian insufficiency (POI), affects 1% of women under the age of 40.[1] A woman is born with several follicles, which, after the end of puberty, range from 300,000 to 400,000 in both ovaries. The ovaries also produce the hormones estradiol and progesterone, which regulate menstruation and ovulation. Around the age of 40-45 years, the female begins to transition from the reproductive to the non-reproductive period of her life. For some women, however, this process onsets earlier than expected. Menopause comes prematurely to 1/250 women under the age of 30 and 1/100 women under the age of 40. The majority of women who present premature ovarian insufficiency have enjoyed normal puberty, and have had regular cycles. Different situations can induce menopause such as radiotherapy, chemotherapy, or the surgical removal of the ovaries and primary ovarian insufficiency where menstruation is suddenly permanently discontinued.[2]

Beyond the crucial role of estrogens in the reproductive capacity of the woman, there are also many other, and equally important, functions such as raising HDL cholesterol, reducing LDL cholesterol, causing vasodilation, and protecting against osteoporosis. A premature reduction in estrogen places females at a higher risk for cardiovascular disease, parkinsonism, depression, osteoporosis, hypertension, weight gain, midlife diabetes, as well as cognitive disorders and dementia, such as Alzheimer's disease (AD). Estrogens also affect cortisol levels and their effectiveness, the hypothalamic-pituitary-adrenal (HPA) axis, the neurotransmitters serotonin and acetylcholine, neurotrophic factors, and neuronal plasticity as well as synaptic function. Estrogens seem to prevent cognitive disorders arising from a cholinergic deficit in women and female animals in premature menopause that affects the central nervous system (CNS).[1]

A literature search was conducted on cognitive disorders in menopausal women and animal models, focusing mainly on premature menopause. We searched PubMed articles published during the last 25 years using the keywords: menopause, premature menopause, premature ovarian insufficiency, and cognitive disorders

Results & Discussion

Causes of premature menopause

The causes that lead to premature menopause have not been precisely determined. The risk factors that increase the likelihood of premature menopause is family history (with the risk increasing by up to 12 times, without, of course, this being a rule, since several investigations reveal that only 50% of women with premature menopause have had a family history), smoking, and epilepsy. Smoking demonstrates an antiestrogenic effect and seems to be associated with the occurrence of premature menopause. Some other studies suggest that women with autoimmune diseases, such as Hashimoto's thyroiditis, diabetes, or rheumatoid arthritis, are at higher risk for premature menopause as well. In these diseases, the body produces autoantibodies in one or more organs. As these antibodies may attack against, for example, the thyroid, causing this gland to be dysfunctional, they can also attack ovaries precipitating premature menopause.[3] (Table 1)

Table 1: Causes of premature menopause

Genetic abnormality	Two functioning X chromosomes are needed for normal ovarian function. Some genetic conditions involve problems with X chromosomes such as: Turner syndrome (one of the X chromosomes is missing or abnormal) Fragile X syndrome (where the bottom of the long arm of the X chromosome is broken or fragile) Women who have Turner's syndrome type XO and those who are carriers for fragile X often have POI.
Autoimmune disorders	Examples include thyroid disease, Type 1 diabetes, Crohn's disease, coeliac disease, and chronic candidiasis (thrush).
Metabolic disorders	These disorders are rare but may include galactosemia and aromatase deficiency (a problem in converting the hormone androgen to estrogen).
Infection	Such as the mumps.
Idiopathic	Idiopathic describes the individual cases of women whose periods stop with no known cause.

Premature menopause and cognitive functions

Most women in menopause (around 70%) report a deterioration of their memory acumen in the peri-menopausal period.[4] Symptoms are related to the stress and depression of this period and present early (usually within the first year after the last menstrual period). Women receiving hormonal replacement therapy seem to improve their memory when the treatment is initiated before their last menstrual cycle.[5] It has not yet been explored whether women who demonstrate cognitive disorders during their menopause are more likely to experience mental disorders or dementia at an older age.

Mild Cognitive Impairment (MCI) in the perimenopausal period

It is important to remember that MCI is considered a very early stage of dementia and that dementia is very rare in people younger than 50 years of age. The dementia risk progresses with age, reaching 65% for individuals 65 years of age or older.[6]

Alzheimer's disease (AD) is the most common type of dementia, but there are others such as vascular dementia, frontotemporal, and dementia with Lewy bodies. In some women with MCI dementia never is established and their condition improves over time. Depression may be present in MCI patients and is difficult to ascertain whether it is the depression that is causing the memory dysfunctions or whether women with MCI are at a higher risk to experience depression. Evidence has been presented that depression may be the first manifestation of cognitive decline.[7]

Mechanisms underlying the relation between premature menopause and cognition

Hormonal disorders affect brain function both directly, by leading to cognitive impairment, as well as indirectly, by causing emotional disorders, sleep disorders, as well as burning sensations and redness in the face.

Estrogens, through β-receptors, affect the activity of serotonin and of the hypothalamic-pituitary-adrenal axis (HPA), leading to increased levels of cortisol and cortisol activity, resulting in phenomena of stress, depression, burning sensations, and redness, as well as cognitive disorders.[8-11]

A study conducted in early postmenopausal women (around 52 years of age) demonstrated that the effect of estrogen on serotonergic function is most likely to be the main mechanism that links cognitive decline with the observed emotional disorders, the reduction of serotonin implicated in the emergence of these emotional disorders, as well as a pronounced decline in verbal memory, but not spatial memory.[12] Another study, employing Positron Emission Tomography (PET), led to the conclusion that substitution treatment with transdermal estrogen led to a significant increase in the binding ability of serotoninergic receptors, especially in the right frontal lobe (5-HT 2), and improved the psychomotor condition of patients.[13]

Cognitive decline rebounds as a direct consequence of the decrease in estradiol. Experimental models have shown that estradiol protects from the emotional and cognitive disorders resulting from the reduction of serotonin. Furthermore, estrogens seem to protect against cognitive disorders arising from a cholinergic deficit in women and female animals in middle age. These studies suggest that the decrease in midlife estrogen levels results in changes in cholinergic and serotonergic activity, which, in turn, contribute to emotional and cognitive disorders.[14]

However, these experimental models are usually created by surgically removing the ovaries and these conditions are not identical to premature or normal menopause during which, unlike experimental models, the production of LH, FSH, GnRH, and testosterone does not cease altogether.[15]

Estrogens, besides their effect on the levels and activity of neurotransmitters, also promote the growth of neurons and the formation of synapses, acting as antioxidants and regulating the homeostasis of calcium and the secondary messenger systems.[16-20]

During menopause elevated cortisol levels and increased cortisol activity are presented. This may be connected with the incidents of burning sensation and redness, as an excessive reaction to stressful stimuli (which estrogen appears the balance these out), disturbances in the verbal memory, and worsening of the presentation of mnemonic goals. We could claim that there is a connection between cortisol, stress, and cognition; however, this hypothesis has not been extensively tested in cases of premature menopause.[21] Notably, the effect of age on cortisol activity appears to be three times higher in women than in men.[22]

The age and the general health condition may affect the effects of sex hormones on cognitive functions. Experimental models have demonstrated that early administration of estrogen at the onset of menopause helps mental functions, something not achieved in delayed administration of them.[23] In observational studies, the early administration of estrogen improves memory and hippocampus function in later life.[24]

The deterioration of the cardiovascular risk factors that accompany the peri-menopausal period may be a further route through which cognitive functions deteriorate with age. Cardiovascular factors are also risk factors for cognitive disorders

and dementia during midlife and old age. As a consequence, women with premature menopause and cardiovascular aggravating factors are at an even higher risk for the occurrence of mental disorders that can lead to dementia. It should be noted that the underlying pathology of dementia begins more than ten years before the onset of clinical symptoms of the disease.[25]

The most common forms of dementia in the elderly are Alzheimer's disease and vascular dementia, which are two different disease entities. Nevertheless, cardiovascular diseases are pathogenetically linked to cognitive impairment and dementia regardless of the type, with vascular pathology existing in, at least, half of the patients with dementia.[26] Additional studies, correlating clinical and neuropathological findings, seem to support the notion that the clinical deterioration of Alzheimer's disease is more rapid when it coexists with vascular disease.[27] The Framingham Stroke Risk Profile scale reveals the relationship between vascular risk factors and cognitive deficits.[28]

Studies in Finland have shown that hypertension and hypercholesterolemia in middle-aged people (around 50 years of age) can result in mild cognitive impairment (MCI) or Alzheimer's disease that is going to be present 20 years later. This is the reason why studies have explored whether these two factors could be considered preclinical dementia markers.[29] The relationship between midlife hypertension (frequently encountered in premature menopause) and old age dementia has been demonstrated in studies completed in Sweden and Hawaii.[31]

Increased body mass index (BMI) at the age of 50 has been associated with an increased incidence of dementia in old age, while the same event at the age of 65 shows no statistically significant relationship. Yet, we must remember that estrogen is stored in the fat tissue so women with lower BMI have a greater chance of early menopause while women with higher BMI usually experience menopause later in life.[32-34]

Regarding diabetes, when it appears before the age of 65 (but not after), it seems to be associated with the occurrence of mild cognitive disorders or dementia. Diabetes longer than 10 years has also been associated with the occurrence of mild cognitive disorders.[34-35] Finally, there is also ischemic leukoaraiosis which has been associated with mental disorders mainly of the frontal type (e.g. designing, using strategies, and changing objectives).[36]

Conclusion

Premature menopause affects the CNS directly and indirectly, both transiently and in the long term, leading to cognitive impairment and even dementia, mainly due to the decreasing estrogen level and comorbidity with cardiovascular risk factors, autoimmune diseases, and aging.

Conflict of interest

The authors declare no conflict of interest.

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