MEGA JOURNAL OF CASE REPORTS

OPEN ACCESS

Short Communication

Compiled Date: August 06, 2024

Possibilities of Menopause Hormonal Therapy in Healthy Brain Aging in Women

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Abstract

After the collapse in prescribing for menopausal hormone therapy (MHT) that led to the publication in July 2002 of the first results of the WHI (Women's Health Initiative) study throughout the world, little by little and during the following two decades, a multitude of studies and clinical trials have been appearing that are consolidating the idea that the benefits far outweigh the risks derived from its use. Recently, due to the increase in life expectancy in all industrialized countries around the world, the study of neurodegenerative diseases is taking on more and more interest. At the same time, results have been appearing about the influence that the use of MHT by different means, with different products can have on the risk of those diseases that will greatly condition the future of our long-lived populations and the consequent health care that will be necessary implement to fully respond to these epidemiological events. This clinical note only superficially verifies the positive influence that MHT has on reducing the risk of the appearance of all these neurodegenerative diseases, with data from very different populations, always coinciding, however.

Keywords: Hormone therapy; Menopause; Estrogens; Neurodegenerative diseases; Alzheimer's disease

Introduction

As the first quarter of the 21st century draws to a close, social evolution is undoubtedly conditioned by the ageing of populations around the world. With people's interests constantly changing, there is a growing interest in medicine in diseases that affect healthy longevity and, perhaps spurred on by the still recent CoVID-19 pandemic, mental health is becoming more and more prevalent in our Western societies that are ageing every day. Almost completely past the negative consequences of the Women's Health Initiative (WHI) macro-study, Menopausal Hormone Therapy (MHT) is flourishing and reappearing with new approaches and new impulses resulting from the most recent research. The aim of this brief clinical note is to briefly review the possible associations between gonadal steroids and their functions in the brain during the Menopausal Transition (MT), addressing issues related to sleep disorders, mood disorders in women during this period of their lives, as well as the main neurological diseases that will affect their age development until senility. We will also address whether MHT plays a role in healthy brain aging, through its influence on some neurodegenerative diseases.

MHT beyond the Climacteric Syndrome

With everyone committed to achieving healthy longevity, with regard to brain aging, psychiatry itself is urging us to spend more time and dedication in menopause consultations; the authors of a documented work said that both women themselves and their health professionals who are considering MHT need to weigh up the risks and benefits on an individual basis, which goes beyond a “brief clinical interview that assesses menstrual bleeding patterns and stressful life events” [1]. In the same sense, we ourselves argued that the publication of some studies that linked MHT with the reduction of depressive symptoms encouraged a climacteric and menopause consultation with more focus on the search for clinically significant depressive symptoms and, consequently, offering women MHT when there are still moderate vasomotor symptoms, or when we are faced with a case with risk factors for bone mass loss or fragility fractures [2]. The door is thus open to the consideration of possible new indications for MHT during the menopause.

Menopausal transition and sleep disorders

The associations of more awakenings during sleep with lower levels of E2 (estradiol) and higher levels of FSH (Follicle-Stimulating Hormone) support a condition of sleep discontinuity associated with perimenopause. This is related to changes in female reproductive hormones, so frequent during the years of MHT, independently of nocturnal vasomotor symptoms and depressive symptoms, to which, however, they have often been associated [3]. It is not uncommon in fact for certain forms of insomnia to anticipate vasomotor symptoms and accompany menstrual disorders during this period of a woman's life. Regulating menstrual cycles during MHT with hormonal treatments also regulates sleep when estrogenic fluctuations have undoubtedly succeeded in destabilizing it. This may represent a healthy way to perform TM without suffering the consequences of these hormonal fluctuations.

Depression is more prevalent during MT

When establishing psychosocial and health-related risk factors for depressive and/or depression symptoms during MT, sleep disorders, already discussed, have been pointed out as well as vasomotor symptoms of climacteric syndrome. Thus, it is concluded that treatment for depression or depressive symptoms during peri- and early postmenopause includes the use of standard antidepressants, as well as MHT and behavioral

modifications of sleep and exercise patterns [4]. Indeed, many longitudinal studies, conducted worldwide and in diverse populations, confirm that women are 2 to 5 times more likely to experience a depressive disorder during perimenopause as in the late premenopausal years. Screening for depressive symptoms or disorders in the primary care setting is recommended and can be easily achieved with standard patient-rated scales. The authors of the paper highlight that the higher prevalence of depression and depressive symptoms during TM is due to at least two other specific clinical entities: depression particularly associated with hormones and, on the other hand, psychosocial-dependent depression [5]. MHT necessarily plays a role in this type of disorder.

Suicide risk during depression

Medicine has come too late when the patient achieves his goal of suicide; in depression this risk is significantly increased. To this extent it can influence the well-being of the woman during her MT and because of its capital importance when it finally happens it must always be taken into account [8]. In fact, a study carried out on 45,177 women who underwent periodic health checks between 2015 and 2018 at Kangbuk Samsung Hospital in Seoul, revealed an Odd Ratio (95% CI) for suicidal ideation according to menopausal status of 1.33 (1.20-1.48), 1.15 (1.00-1.33) and 1.61 (1.38-1.87) for early MT, late MT and postmenopause, respectively [7]. MHT in the presence of climacteric syndrome can also help in this area of situations.

Alzheimer's Disease (AD) and brain aging and MHT

Steven Jett and colleagues described the effects of menopause on ß-amyloid (βA) deposition in the brain using Pittsburgh compound B-PET (PiB-PET) studies, which show the menopausal status and effects on βA deposition. They describe that βA deposition is progressive during the MT period, as evidenced in a representative case that underwent PiB-PET at baseline when the patient was perimenopausal and 3 years later when she was already postmenopausal [8]. Just a few years earlier, the potential sequence of pathological events that occur at the mitochondrial level during aging and the so-called “critical time” of E2 decline in the female brain had been described [9]. The paper describes the demonstration that E2 increases the activity of the Electron Transport Chain (ETC), stabilizes the Mitochondrial Membrane Potential (MMP), prevents the production of Reactive Oxygen Species (ROS) and improves basal respiration and the production of ATP levels, all of which would explain the mechanism of interaction of E2 with the brain-derived neurotrophic factor and Sirtuin 3 that would act as protectors of the cell from harmful ROS of the mitochondria, the basis of neuronal cellular aging. To these pathophysiological bases we must add epidemiological data. In this regard, in May 2021 a study compared six different age groups (60-64 years, 65-69, 70-74, 75-79, 80- 84, and 85-89), in women who were prescribed at least one MHT approved by the American National Agency for the control of drugs and medicines (FDA) [10]. Well then, the instantaneous risk ratios by age that indicate a reduced risk of AD differ significantly among women who were prescribed MHT in a significant way, as age advances; in fact, in the first three age ranges analyzed there are hardly any differences, which are much more noticeable in the remaining three, in which AD becomes epidemiologically more present. Using the same analysis, the authors report an identical finding for age-specific hazard ratios indicating a reduced risk of non-AD dementia in women prescribed at least one FDA-approved form of MHT.

MHT in the risk and evolution of neurological

diseases

The same recent publication, methodologically impeccable, summarizes the implications for precision hormone therapy in the association between its use and the risk of neurodegenerative diseases[10]. The authors start from the analysis of databases that gather 1.5 million women who took MHT or were not subjected to this treatment. After different analyses, they finally compared the data of 189,676 women who had used MHT against another 189,676 who had not been exposed to this type of therapy. Comparing the data of both groups, they analyzed the Relative Risk (RR) of combined Neurodegenerative Diseases (NDD), which included Alzheimer's Disease (AD), Parkinson's Disease (PD), dementia, Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS), and they demonstrate a statistically significant association between the use of MHT and the reduction of the RR of all the diseases described; The results are summarized in **Table 1**. Aside from the statistical significance for all diseases, it is worth noting the relatively low Number Needed to Treat (NNT) with MHT needed to prevent a single case of Alzheimer's disease or any neurodegenerative disease of those analyzed by the authors.

Table 1: Relative risk (RR) of combined Neurodegenerative Diseases (NDD), Alzheimer's disease (AD), Parkinson's disease (PD), dementia, non-Alzheimer's dementia, Multiple Sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS) in users of menopausal hormone therapy (mod. from quote **[11]**).

Disease considered	RR (95% CI)	NNT	p level
All neurodegenerative diseases	0.42 (0.40 to 0.43)	21,56	<0.001
Alzheimer’s diseases	0.43 (0.41 to 0.48)	61,81	<0.001
Parkinson’s diseases	0.47 (0.43 to 0.51)	226,3	<0.001
Dementias	0.41 (0.40 to 0.43)	25,22	<0.001
Non-Alzheimer's dementia	0.40 (0.39 to 0.42)	40,01	<0.001
Multiple sclerosis	0.53 (0.48 to 0.62)	855,9	<0.001
Amyotrophic lateral sclerosis	0.42 (0.28 to 0.63)	4.215	<0.001

CI: confidence interval. NNT: number needed to treat.

It is worth mentioning that the authors found significant differences, always in favor of risk reduction for any form of MHT, regardless of whether natural estradiol was used or conjugated estrogens, even synthetic ones, or esterified estrogens or estrogen salts such as estradiol valerate, or in combinations of estrogens and different forms of progestogens, synthetic or natural, as shown in **Table 2**.

Table 2: Relative risk of suffering from all neurodegenerative diseases as a whole, depending on the type of MHT received and the route of administration used by the users (mod. of quote [11]).

Drug used	Route used	RR (95% CI)	NNT	p level
Estradiol	Tablets PO	0.45 (0.43 to 0.46)	63.164	<0.001
Estradiol	Transdermal patches	0.19 (0.16 to 0.23)	6.553	<0.001
Estradiol	Transdermal patches	0.23 (0.13 to 0.40)	613	<0.001
Estradiol	Transdermal patches	0.54 (0.33 to 0.88)	349	0.01
Estradiol	Transdermal Gel	0.16 (0.09 to 0.18)	877	<0.001
Estradiol	Transdermal Gel	0.22 (0.14 to 0.37)	847	<0.001
Estradiol	Transdermal Spray	0.21(0.12 to 0.35)	798	<0.001
Conjugated estrogens	Tablets PO or IM injection	0.42 (0.40 to 0.43)	123.982	<0.001
Synthetic ECs	Tablets PO	0.43 (0.31 to 0.61)	898	<0.001
Synthetic ECs	Tablets PO	0.26 (0.15 to 0.46)	524	<0.001
Esterified estrogens	Tablets PO	0.42 (0.26 to 0.67)	480	<0.001
E2 valerate	IM Injection	0.51 (0.30 to 0.86)	319	0.009
CE + MPA	Tablets PO	0.30 (0.26 to 0.36)	6.197	<0.001
TE2 + P4	PO Capsules	0.19 (0.15 to 0.23)	4.865	<0.001

RR: relative risk; CI: confidence interval; NNT: number needed to treat; PO: per os; IM: intramuscular; CE: conjugated estrogens; E2: estradiol; MPA: medroxyprogesterone acetate; TE2: transdermal estradiol; P4: progesterone.

Analyzing the comparisons between different MHT formulations, the advantage of using natural products such as estradiol compared to conjugated estrogens that require treating many more patients to achieve similar effects of reducing the risk of neurodegenerative diseases is notable, verifying the NNT of each group. In the same way, it is noteworthy to see how the risk reduction was significant for dementia from any cause and for Multiple Sclerosis (MS) in women who received oral or transdermal HT, regardless of the route of administration in another analysis that the authors conducted comparing both routes of receiving MHT [10]. Finally, it is noteworthy that the results always point in the direction that MHT tends to improve the risks of suffering from any of the diseases analyzed, regardless of whether one or the other form of therapy is administered, whether by one or the other route is chosen for each situation. They themselves concluded verbatim, stating almost categorically that MHT was associated with a reduced risk of all neurodegenerative diseases, including AD and dementia, with a longer duration of treatment and formulations of natural steroids associated with greater efficacy. In the question of the duration of MHT and its protective effect against AD, these data coincide exactly with another finish publication in which the follow-up of a cohort of more than 8,000 women for 20 years showed a greater protective effect the longer the

treatment time [11]. These findings, the previous authors conclude, promote precision MHT to prevent NDE, including AD [10].

Final Comments

Far away at this point in the 21st century is the (unfounded) fears that the results of a large but poorly planned study caused among gynecologists throughout the Western world [12]. At this time, quality of life is the most important value among health objectives in the management of MHT during MT [13]. In addition, MHT has long demonstrated a reduction in overall mortality and with marked consistency of results for this objective for all causes with ET (Estrogen Therapy) or MHT for at least 5 years of persistence in women whose age of onset is less than 60 years. These data should be a general and prominent part of the offer of MHT treatment in menopausal consultations throughout the world.

In conclusion from what has been noted so far, we propose some final, summarized reflections, taken from others that we expressed in a recent publication [14] and that we reproduce here:

- All available evidence from cross-sectional studies suggests relationships between menopause, depression and subsequent cognitive deficits.
- Longitudinal studies with very different populations frequently point in the same direction.
- MHT appears to improve all depressive symptoms and reduce the RR of depression diagnoses.
- There is some evidence that MHT reduces the risk of developing dementia and Alzheimer's disease, as well as other neurodegenerative diseases.
- The administration of natural estrogens seems to be preferable to synthetic estrogens, in terms of reducing the RR of neurodegenerative diseases.
- No significant differences appear to be observed in this reduction when analysing oral or transdermal routes of administration of MHT.
- There are mechanisms of biological plausibility that can explain all these actions of estrogens at the brain level.
- Prospective and well-designed RCTs (randomized clinical trials) are necessary to allow us to advance in these areas in the future.

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Citation of this Article

Neyro JL, Espitia De La Hoz FJ and Palacios S. Possibilities of Menopause Hormonal Therapy in Healthy Brain Aging in Women. Mega J Case Rep. 2024;7(8):2001-2007.

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