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original article

Hormone replacement therapy and mild cognitive impairment in postmenopause

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SUMMARY: **Hormone replacement therapy and mild cognitive impairment in postmenopause.**

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The mild cognitive impairment (MCI) is an impairment of cognitive abilities that not yet satisfies diagnostic criteria of dementia. Impaired cardiovascular parameters are associated with the risk of cognitive disorders. Low estrogen levels in postmenopause are related to impaired ability of the central nervous system and could explain the high incidence of cognitive disorders in postmenopausal women. The aim of this study was to assess cognitive performances in postmenopausal women affected by MCI and the impact of an HRT combination of low-dose oestradiol plus drospirenone. The evaluation of cognitive skills performed with neuropsychological tests showed that women on HRT had higher cognitive performances than controls, in particular they showed higher rates of short and long term memory, attention, verbal fluency and visuospatial performance. These ability are typically involved in the MCI. The beneficial effects of drospirenone on cardiovascular parameters could explain the reduce risk of developing dementia.

RIASSUNTO: **Terapia ormonale sostitutiva e deficit cognitivo lieve in postmenopausa.**

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*Il deficit cognitivo lieve (*Mild Cognitive Impairment*, MCI) definisce un deficit delle capacità cognitive che non soddisfa ancora i criteri della demenza. I fattori di rischio cardiovascolare sono associati alla probabilità di sviluppare deficit cognitivi. L'ipoestrogenismo post-menopausale è potenzialmente correlato al deterioramento delle attività del Sistema Nervoso Centrale e potrebbe spiegare l'elevata incidenza dei deficit cognitivi nella post-menopausa. Sono state valutate le* performance *cognitive di 80 pazienti in post-menopausa da almeno 36 mesi affette da deficit cognitivo lieve, suddivise in un gruppo in HRT (estradiolo a basso dosaggio + drospirenone) e in gruppo controllo. L'analisi delle funzioni cognitive effettuata con test psicometrici ha evidenziato, nel gruppo in HRT rispetto al gruppo controllo,* performance *migliori di memoria a breve e a lungo termine, fluenza verbale, attenzione e abilità visuospaziali, capacità tutte coinvolte nel MCI. L'effetto benefico del drospirenone sui fattori di rischio cardiovascolare potrebbe spiegare il ridotto rischio di sviluppare demenza.*

KEY WORDS: Mild cognitive impairment - Menopause - Drospirenone.
Deficit cognitivo lieve - Menopausa - Drospirenone.

Introduction

Mild cognitive impairment (MCI) identifies a dynamic transitional state between normal ageing and dementia (1). It is characterized by the impairment of various domains of cognitive performances (memory, attention, language, executive function, visuospatial abilities), not yet satisfying the diagnostic criteria for frank dementia (1, 2).

A large body of experimental data support a positive effect of oestrogen and progesterone on neuronal function, neurotransmission systems and interaction with neurotrophic factors (3-5). Postmenopausal hypoestrogenism involves relevant modifications in

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the neurotransmettitors, neuropeptides and neurosteroids levels. Such events are potentially linked with the decline of cognitive activities of the central nervous system(CNS), and may explain the high incidence of cognitive impairments in postmenopause (6, 7).

Clinical data about the influence of the HRT (Hormone Replacement Therapy) on cognitive impairments are conflicting: some Authors showed a beneficial effect of the HRT on global cognitive performances (8, 9) and on specific functions such as memory and language (10, 11), others failed to show any effect (12-14). To date data about the relationship between HRT and MCI are lacking. The aim of our study is to evaluate the effect of HRT, taken at least for two years, on cognitive performances in postmenopausal women with MCI.

Materials and methods

Eighty patients aged between 50 and 57 years were recruited. All were in postmenopause lasting at least 36 months (FSH> 40 UI, 17-beta oestradiol < 20 pg/ml) and affected by MCI. As assessed with the following tests: 15 Ray's words test (Ray's test 1958), digit span (Wechsler, 1945, 1955,1981, 1987), test of phonetic and semantic verbal fluency (Spinnler & Tognoni, 1987), Trail Making test A, B, diff B-A (Reitan, 1958).

Exclusion criteria were: frank dementia assessed with MoCA test score< 23 or >26 (Nasreddine et al., 2005), depression and/or mental diseases assessed with HDRS test score >10 (Hamilton 1960), neoplastic disease, hypertension, anemia, hormonal disorders (diabetes, dysthyroidism, cortico-adrenal deseases), known psychiatric illness, drugs/alcohol addiction, deficit of vitamin B12, practice of competitive sports, no regular eating customs.

The cognitive performances were compared in two groups of patients:

- group A: 30 women taking HRT with 17-beta-estradiolo 1 mg + drospirenone 2 mg at least from two years;
- group B (control group): 50 women in postmenopause not taking HRT.

The statistical analysis was performed with SPSS Statistical Package for Social Science for Windows version 17.0. The data were analyzed as descriptive data; the averages of variables were compared using the Student's t and analyzed for variance (ANOVA). Statistical significance was set at $p < 0.05$. To standardize the results of various psychometric tests, a "Cognitive Composit score" was set up for the functions of attention and memory (Score Composit A) as the sum of z scores of the 15 words of Rey Test, Digit span forward and backward, phonemic and semantic verbal fluency test, and a "Cognitive Composit score" was set up for executive functions (Composit Score B) as the sum of z scores of the Test TMT a, B, BA diff. A single "Cognitive Composit score" was not set up because not all psychometric test scores had the same trend of reading.

Results

The two groups were homogeneous as regards age (group A 52.7±2.73 vs group B 52.8±2.29), BMI (group A 24.9±2.6 vs group B 25.8±3.3), duration of menopause (group A 40.8±5.13 vs group B 42.3±4.76). The global psychometric evaluation excluded frank dementia and depression in both groups: in fact they were homogenenous in the MoCA test (group A 24.03±0.81 vs group B 23.76±0.72) and in the HDRS (group A 6.07±2.79 vs group B 5.63±2.82).

The analysis of cognitive functions, obtained with psychometrical tests, showed that the group under HRT had higher scores as compared to controls (Figures 1 and 2). In particular, in group A the 15 Ray's word test showed higher performances in short and long term memory and in attention (Ray immediate rievocation: group A 39.66±2.89 vs group B 32.16±5.20; Ray delate rievocation: group A 8.69±2.30 vs group B 5.42±1.35), the verbal fluency test showed more wideness, organization and ease to access to the phonological and semantic lexicon (fluency for letter: group A 37.80±5.46 vs group B 27.83±4.33; fluency for categories: group A 38.00±4.33 vs group B 32.53±3.15), the TMT A, B, diff B-A, that evaluate the ability of the spatial planning in a visuo-motorious task, showed higher executive performances (TMT-A group A 43.60±11.64 vs group B 79.40±16.44, TMT-B group A 91.43±19.0 vs group B 161±45.60, TMT- B-A group A 47.83±21.7 vs group B: 81.66±44.27), the forward and backward digit span showed higher performances of attention (forward digit: group A 6.69±0.88 vs group B 5.28±0.81, backward digit: group A 5.39±0.63 vs group B 4.38±0.68).

Discussion and conclusions

The MCI is the most common cognitive impairment, with a prevalence in over sixties population of 1-15%. The MCI is a dynamic state that could

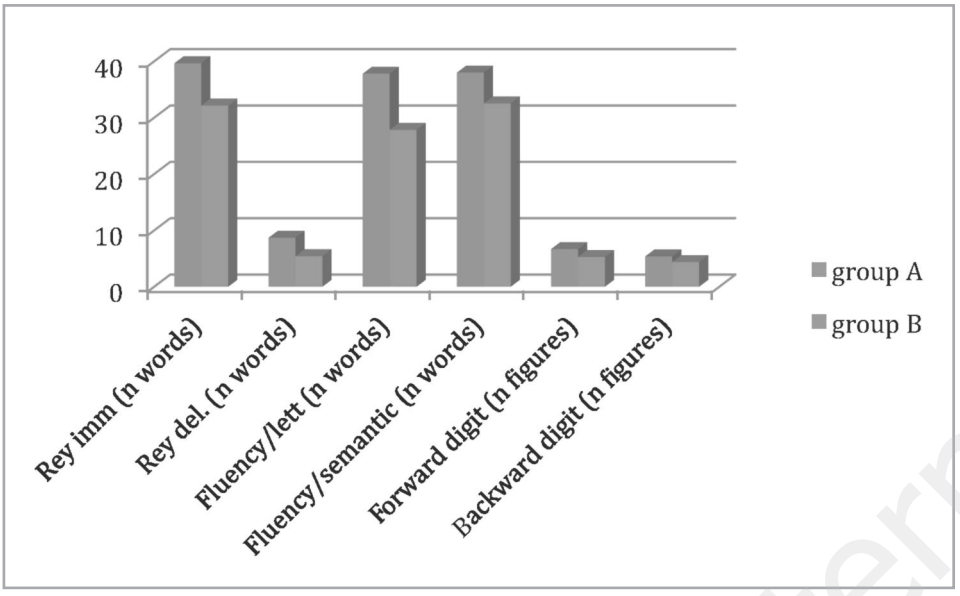

Fig. 1 - Psychometric analysis for the assessment of cognitive domains of memory and attention.

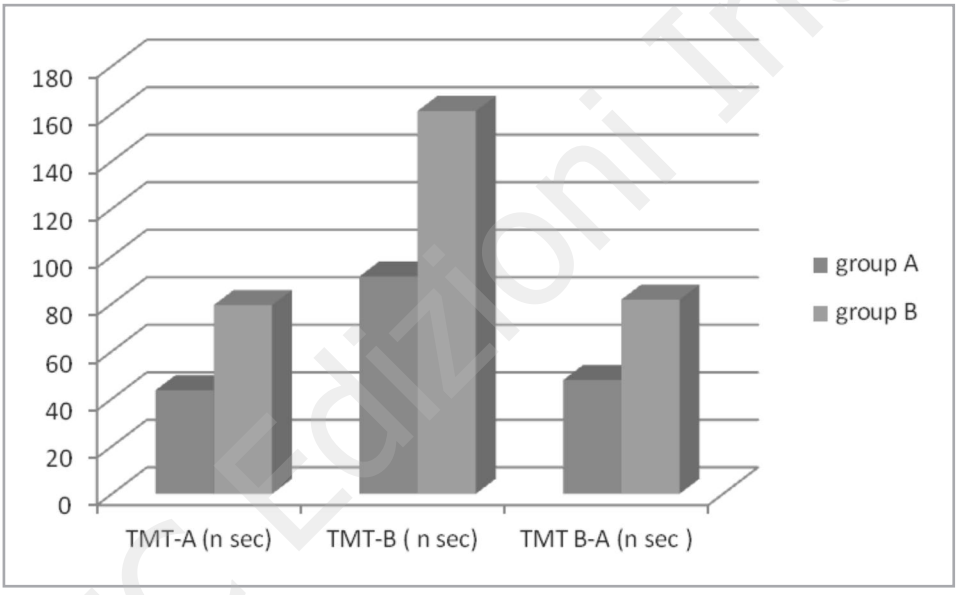

Fig. 2 - Psychometric analysis for the assessment of cognitive domains of executive ability.

progress to dementia or not, therefore is very intriguing the hypothesis of a pharmacological intervention on the progression to dementia (1). The most common age for onset of MCI is menopausal transition: the decrease steroids levels occurring in the postmenopause represents an increasingly relevant risk factor for the onset and progression of the MCI. Higher oestrogen levels are associated with less cognitive impairment, independently of age at menopause and BMI (4). Observational studies showed a relationship between HRT and significant reduction of the risk for dementia; in particular some Authors showed a positive effect of the HRT on short term verbal memory and on some domains of the executive function (12, 13). Nowadays data are lacking as regards the association between MCI, postmenopause and the effect of a long-term HRT. In addition, adequate data are not available about the relation between HRT and specific cognitive functions.

Our study showed that the cognitive performances of postmenopausal patients with MCI on HRT are

better than patients who had never used therapy. Moreover, a clear difference was observed in the ability of short and long term memory, in visuospatial abilities and executivity, in language (phonological and semantic fluency) and attention between group using HRT and controls. Therefore, patients using HRT have a less impairment of the cognitive function that are modified in the MCI, in contrast with patients who had never taken HRT. Such data confirm a beneficial effect of the therapy on cognitive performances. Compared to previous works, in our study potential interfering bias were excluded: confusing factors such as dementia, depression and cardiovascular risk factors, large range of age, short time since menopause associated with the disequilibrium typical of the perimenopausal state.

A high cardiovascular risk, mainly in postmenopause, is correlated to a decline of cognitive abilities (15); in fact women with a higher cardiovascular risk are more prone developing dementia. In this view, the choice of HRT should be targeted towards low dose of oestrogens and to progestins with low metabolic effects to limit the negative effects on cardiovascular risk factors. Recently, a new synthetic progestin (drospirenone) has been introduced, differing from the others classical progestins because its antimineralcorticoid and antiandrogenetic properties (16, 17). The HRT with drospirenone has been showed to significantly reduce systolic and diastolic blood pressure in hypertensive postmenopausal women, in addition it could contrast the android distribution of the adipose tissue, and has a beneficial effect on fat's metabolism, improving metabolic parameters in patients affected by metabolic syndrome. For these reasons, the use of drospirenone is preferred in women with relevant cardiovascular risk (18). The HRT administered in our study was 17-beta oestradiol associated with drospirenone, because of its beneficial effect on cardiovascular risk factors and, as a consequence, on the risk of developing dementia.

Our study shows some limits: basal clinical and psychometric evaluation before HRT was lacking, the sample of patients was small, the length of therapy was not as long as to clarify the long term effects on cognitive performances. In this view, a prospective study could clarify the role of the HRT on the prevention of cognitive impairments in postmenopausal women.

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