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Hyperhomocysteinemia in menopausal hypertension: an added risk factor and a dangerous association for organ damage

R. NOTO, S. NERI, G. MOLINO, S. MELI, P. NOTO, B. MAUCERI, D. CILIO, A. RAPISARDA, Z. NOTO

Department of Internal Medicine and Sistemic Diseases, University of Catania, School of Medicine - Catania (Italy)

Abstract. – **Hyperhomocysteinemia is widely recognised as an emerging risk factor of endothelial dysfunction and vascular damage. In this study we wanted to verify if it, when associated to arterial hypertension – traditional risk factor – represents a higher added risk of organ damage during menopause, which is a condition connected to a higher incidence of cerebrovascular diseases.**

A survey of 30 postmenopausal women with similar characteristics (BMI, age, absence of relevant pathologies such as diabetes, metabolic disorders and absence of smoking) was selected (menopause had occurred from 12 to 16 months at the moment of observation). At the moment of the observation they had not gone through any continuous pharmacological therapy. They were subdivided into 3 groups: normotensive; hypertensive (with 2nd degree hypertension: mild to moderate) without organ damage; hypertensive with organ damage (TIA, ischaemic heart disease, etc.). The carotid IMT, measured with ultrasound method, was considered as an organ damage parameter. 43% of the patients had high levels of homocysteine (> 15 µmol/l), which are levels considered at risk in other surveys. The highest levels of homocysteine were recorded in hypertensive women with episodes of acute cerebrovascular damage (µmol/l = 24.3 ± 8.9). In this group, a positive correlation (r = 0.7) was obtained between homocysteine levels and carotid IMT. The possible coexistence of hyperhomocysteinemia and arterial hypertension, even though without particularly high values for both of them, in menopause may represent a dangerous association responsible for a significant organ damage and, therefore, for acute cerebrovascular events.

Key Words:

Hypertension, Menopause, Hyperhomocysteinemia, Carotid IMT.

Introduction

Recent relevant scientific data have definitely clarified the importance of cerebro-cardiovascular risk stratification in the evaluation of prognosis of hypertensive patients[1,2,3]. This evaluation, at present, is made not only in terms of hypertensive severity, but also related to other risk factors and mainly to the coexistence of possible organ damage. In this context menopause may be included, in which the incidence of cerebrovascular pathologies is well known and consolidated[4-7] also for the association, at times, of several risk factors, some of them are already well-known (arterial hypertension, lipid metabolic disorders, diabetes, etc...)[5,6,8-10], some others recently identified (endothelial dysfunction, adhesion molecules, hyperhomocysteinemia, etc.)[11-17].

In this study we wanted to verify whether the possible coexistence of hypertension and high levels of homocysteine in menopause may induce a precocious organ damage and a higher risk for cerebrovascular acute pathologies and, therefore, whether hyperhomocysteinemia may represent a useful marker for a correct risk stratification.

Materials and Methods

Among our Internal Medicine check-ups carried out in pre- and menopausal women, in this last year we have identified a survey, which, even though limited in number, considered a group of women homogeneously se-

lected. The 30 patients of the survey presented menopausal conditions from 12 to 16 months before the moment of observation. The age and other anthropometric data (BMI) were analogous (absence of obesity, smoking, diabetes, metabolic disorders), as well as diet. In the survey we included women with normal arterial pressure, and women who developed hypertension within few months after menopause. In the latter case we included only women with mild to moderate hypertension (160-179/100-109 mmHg) and women without pressure profiles particularly at risk (pressure variability, high percentage of systo-diastolic peaks, non dippers), valued through Ambulatory Blood Pressure Monitoring (ABPM) checked, after an adequate interval, a second time. We also included only women without relevant pathologic conditions, except hypertension. Patients, after the evaluation of both the previous clinic-anamnestic parameters and the ones verified by us (routine biohumoral, ECG, echocardiography, etc.), were subdivided into 3 groups: normotensive; hypertensive, (with hypertension occurred during menopause), who were further subdivided into 2 subgroups: one with documented recent episodes of acute cerebrocardiovascular damage (ischaemic heart disease, TIA, etc.); a second one with no episodes of cerebrovascular damage. No patient had undergone any continuous pharmacological treatment until the moment of observation.

The carotid IMT, valued with echocolordoppler method, was considered as an indicative organ damage parameter, valuable at present as confirmed by a number of researches[18-23]; according to reliable studies, the normal value of the carotid IMT is up to 1 mm[21].

The survey is shown in Table I. The routine biohumoral exams were carried out with traditional methods. ABPM was carried out with AND TM 24 30 instruments, the echocolordoppler with ATL 800.

The dosage of homocysteine was carried out with HPLC method on plasma (5 cc of blood put in a cooled-down polyethylene test tubes, containing EDTA – 0.5 μmol/l), which was kept frozen until the moment of determination (reagents: Polytechne – Livorno, Italy). Statistic analysis was carried out using Student's t test method and the calculation of regression curves.

Results

Results are reported in Figure 1 and in Table II.

The range of homocysteine level variations in all patients of our survey was between 2.63 and 38.85 μmol/l. Levels of homocysteine are considered *normal* between 5 and 15 μmol/l, *moderate* between 16 and 30 μmol/l, *intermediate* between 31 and 100 μmol/l, *severe* > 100 μmol/l.

57% of the patients showed normal levels, 33% moderate levels, 10% intermediate levels; however, levels considered high and at

Table I. Clinical and pressure parameters (valued also with ABPM method) in normotensive (MN), hypertensive without organ damage (MH), hypertensive with organ damage (MH_{OD}) menopausal women (menopause had occurred from 12 to 16 months). Values are expressed also as average ± SD. BMI = Body Mass Index. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. MAP = Mean Arterial Pressure. HR = Heart Rate.

	MN (10)	***MH (10)***	***MH_{OD} (10)***
AGE (years ± SD)	50 ± 2	48 ± 3	50 ± 5
Beginning of menopause (months)	12 ± 3	15 ± 2	14 ± 2
BMI (Kg/m^2)	26 ± 1	26 ± 3	27 ± 1
SBP (mmHg)	136 ± 3.1	160.4 ± 4.6	166 ± 2.2
DBP (mmHg)	74.6 ± 4.1	87.2 ± 5.4	89.3 ± 5.4
MAP (mmHg)	70.4 ± 2.6	76.5 ± 3.2	78.6 ± 2.4
HR (b/m)	68 ± 8	70 ± 4	68 ± 4
Diurn syst peak %	7	14	16
Diurn diast peak %	6	12	11
Noct syst peak %	5	8	10
Noct diast peak %	8	11	12

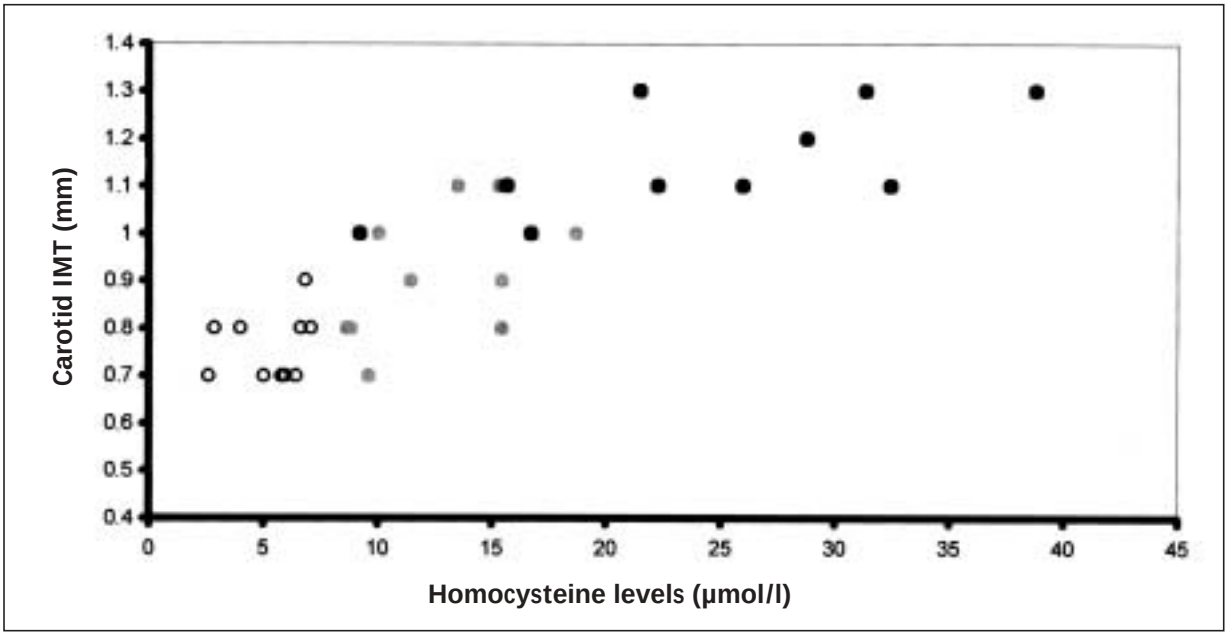

Figure 1. Correlation between homocysteine levels and carotid IMT in menopausal women. (o normotensive woman • hypertensive without organ damage • hypertensive with organ damage).

risk were observed in 43%, altogether, of our patients and this datum agrees with what was found in other surveys.

Subdividing all patients into normotensive (MN), hypertensive without organ damage (MH) and hypertensive with organ damage (MH_{OD}), the mean value of homocysteine was respectively: 5.35 ± 1.64 µmol/l, 12.724 ± 3.4 µmol/l, 24.3 ± 8.9 µmol/l with a significance MN vs. MH $p < 0.001$ and MH vs. MH_{OD} $p < 0.01$. Analysing the correlation between the levels of homocysteine and carotid IMT (Figures 2 and 3), a significant correlation r = 0.5 in group MH and even more r = 0.7 in group MH_{OD} was obtained.

Discussion

Homocysteine, of which the meaning of cardiovascular age-related risk is widely known[24-35], may at times increase in menopause[12-15,36,37]; that seems to be related to the progressive decrease of estrogenic concentration, especially of 17-β-estradiol, which

Table II. Homocysteine levels (Hcy in µmol/l) e carotid IMT (mm) in normotensive (MN), hypertensive without organ damage (MH), hypertensive with organ damage (MH_{OD}) menopausal women

	MN		MH		MH_{OD}	
	Hcy	IMT	Hcy	IMT	Hcy	IMT
1	6.47	0.7	11.46	0.9	31.41	1.3
2	7.11	0.8	13.54	1.1	38.85	1.3
3	2.88	0.8	15.35	1.1	28.82	1.2
4	6.66	0.8	15.47	0.9	32.49	1.1
5	6.86	0.9	18.72	1	22.28	1.1
6	2.63	0.7	8.85	0.8	26.01	1.1
7	5.82	0.7	15.45	0.8	16.74	1
8	5.99	0.7	9.64	0.7	15.69	1.1
9	5.05	0.7	10.08	1	21.51	1.3
10	4.03	0.8	8.68	0.8	9.24	1

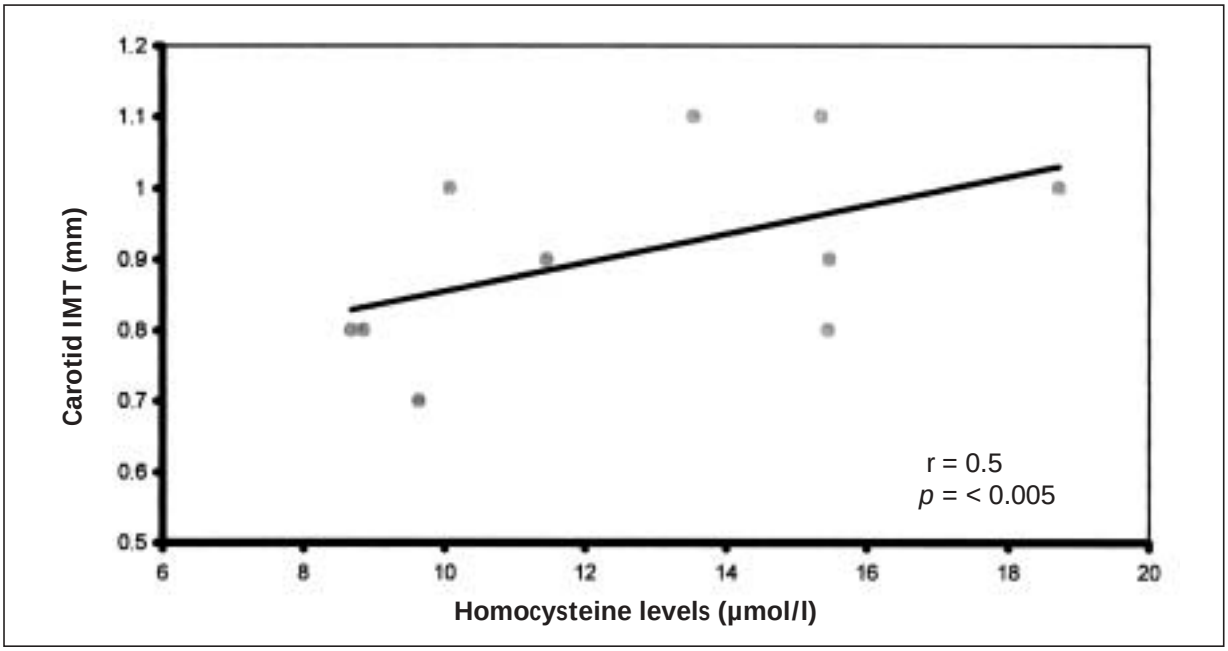

Figure 2. Correlation between homocysteine levels and carotid IMT in hypertensive menopausal women without organ damage.

might interfere with the complex biochemistry of homocysteine, and therefore it is probable that transamination of methyonine – or other enzymatic mechanisms – may be reduced, determining higher levels of homocysteine[11-13,15.] In pre menopausal women, plasmatic levels of homocysteine after a methyonine load are negatively and significantly correlated to levels of 17-β-estradiol[14,38]; moreover substitutive therapy with this estrogen

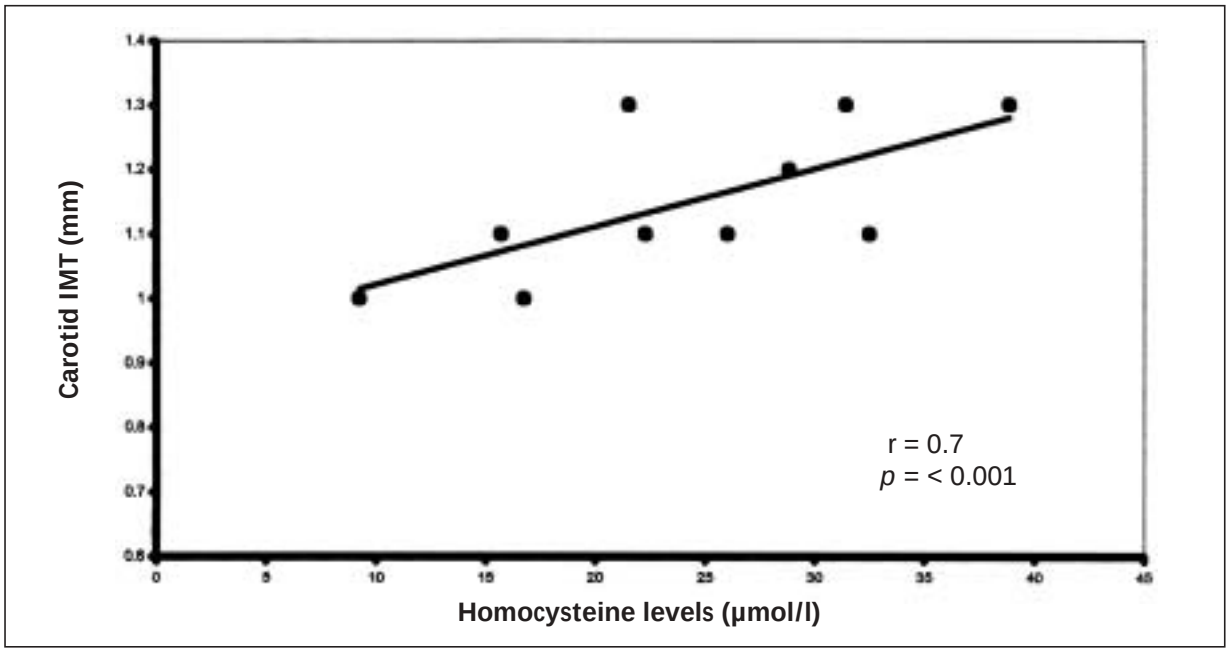

Figure 3. Correlation between homocysteine levels and carotid IMT in hypertensive menopausal women with organ damage.

significantly reduces fasting serum homocysteine levels[36,37]. Data in lots of studies show that levels of homocysteine in about 40% of post-menopausal women are high[15] and our study agrees. Hyperhomocysteinemia is defined as an increase of levels over 30 µmol/l; in fact, lots of studies frequently confirm a moderate hyperhomocysteine is associated to cardiovascular disease and to arterial and venous thrombosis[24,33,39].

Also arterial hypertension is one of the possible risk factors occurring in menopause, and it is widely demonstrated that, even as a sole factor, it is determining in the genesis and progression of vascular damage[4,6,8,10]; this action is correlated to its duration and severity.

In our survey we intentionally wanted to identify mild to moderate hypertensive women, without pressure profiles 'at risk', which could have affected the organ damage progression[40,41,42]. In those women the temporal onset (lasting about 1 year) of hypertension, alone and even if not treated, does not justify an organ damage expressed as an increase of IMT; this parameter resulted within the limits in non hypertensive menopausal women with no elevated homocysteine levels. No one of our patients presented the coexistence of other risk factors nor she was under pharmacological treatment. Only in 10% of our patients a homocysteine level, to be considered dangerous, was present. Many studies, however, seem to show how a cerebrovascular risk is present when homocysteine levels are hardly over normal limits and how a 5 µmol/l increase matches 1/3 risk increase[33,38].

It is sure that in menopause no risk factor may exist, but if arterial hypertension and hyperhomocysteinemia – even if singularly without particularly high values – coexist, a more dangerous association might establish so to quicken a progressive organ damage and worsen clinic manifestations connected.

In conclusion, menopause represents a period of particular clinic attention as several risk factors for cerebrovascular diseases may coexist. Some of them, as hypertension, have been widely analysed, others are being progressively identified. To recognize patients at risk, together with the traditional risk stratification, based on arterial pressure severity, at present other coexisting factors, and mainly organ damage, are being analysed.

There is a scientific reason to consider the carotid IMT one of the added exams in the studies of menopause, especially when it is associated to hypertension. We believe that alterations of this parameter and/or the coexistence of other biohumoral markers (hyperhomocysteinemia, endothelial dysfunction, etc.), which are found in a patient even only with mild to moderate hypertension, might be the cause of a higher cerebrovascular risk and, consequently, induce a more intensive pharmacological treatment. It should not only reduce arterial pressure, but also the possible initial organ damage. In order to identify organ damage and risk stratification, some methods seem to be easily carried out (as the echocolordoppler). Other methods, among which the research of possible presence of hyperhomocysteinemia, need easier clinic procedures, since at the moment the expenses are too high to extend such methods to large numbers of patients.

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