Cognitive functions, apolipoprotein E genotype and hormonal replacement therapy of postmenopausal women

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Abstract

OBJECTIVE: The results of many studies revealed that estrogen plus progestogen therapy (EPT) may modify dementia development risk in relation to the apolipoprotein E gene (APOE) polymorphisms. However, the mechanism and subsequently clinical importance of such an effect are still unexplained. The objective of this study was to explore the influence of EPT on cognitive functioning of women in their postmenopausal life in relation to APOE polymorphism. **METHODS:** The group of 214 women was recruited (106 out of this group with EPT) to the study. The inclusion criteria were: minimum two years after the last menstruation, FSH concentration over 30 U/ml and no dementia signs on Montreal Cognitive Assessment (MoCA). Computerized battery of Central Nervous System Vital Signs (CNS VS) test was used to diagnostic cognitive functions. APOE genotype was performed by multiplex PCR. Statistical analysis was performed using two-way analysis of variance in STATISTICA software. **RESULTS AND CONCLUSION:** The women after menopause have reduced neurocognitive index (NCI) and cognitive functions. NCI and all studied cognitive functions of the patients depended significantly on APOE polymorphisms. The presence of APOE4 corresponded with decreased cognitive functions as opposed to APOE2 which was present in women with better level of cognitive functions. Constantly using EPT correlated with three cognitive functions: memory, verbal memory and processing speed, which were significantly worse for women taking EPT than not taking ones. The interaction between APOE polymorphisms and EPT application was significant only for processing speed. EPT applying women with ε2/ε3 and ε4 obtained better scores in processing speed than women not taking EPT with these APOE polymorphisms. The opposite situation concerned women with ε3/ε3, women taking EPT achieved worse processing scores in comparison with those not taking EPT. It should be noted that APOE polymorphism assessment may be a factor in predicting the effect of EPT on cognitive functioning in postmenopausal period.

ORIGINAL ARTICLE

INTRODUCTION

Hormone replacement therapy (HRT) is a system of medical treatment for surgically menopausal, transgender, premenopausal and to a lesser extent – postmenopausal women. It is based on the idea that the treatment may prevent discomfort caused by diminished circulating estrogen and progesterone, may prolong life and reduce incidence of dementia. In the past HRT was widely recommended in the treatment of menopause and menopausal symptoms as well as in the prevention of osteoporosis, heart diseases and mental dysfunctions (Shuster *et al.* 2010; WHI 2002).

The influence of postmenopausal hormone therapy on cognitive functions and consequently Alzheimer`s disease (AD) development, although attracting considerable scientific interest, remains controversial (Shuster *et al.* 2010). Despite contradictory opinions, some evidence suggests that HRT may modify dementia development risk in relation to the apolipoprotein E gene (APOE) polymorphism (Payami *et al.* 1996; Yue *et al.* 2007; Kang *et al.* 2004).

It is generally accepted that APOE ε4 allele remains the most important genetic risk factor for dementia especially sporadic AD (Carter 2005; Van Duijn *et al.* 1997; Van Duijn *et al.* 1994). The APOE ε4 allele is associated with a 2–3 fold increased risk of getting the disease when one copy is present, and if there are two copies the risk is increased as much as 12 times (the APOE gene is co-dominant). The strong association of APOE genotype to AD is a potent indicator of the importance of lipid metabolism and diet in the pathogenesis of the disease. Among the genetic markers the APOE gene has been widely examined because of its well-documented role in AD and vascular diseases. A number of reports on human longevity show that APOE ε4 allele frequency is lower in older age groups than younger or middle-aged subjects (Van Duijn *et al.* 1997).

ApoE is a polymorphic glycoprotein that plays an essential part in binding to receptors for the uptake of chylomicrons and VLDL remnants and of LDL. The three major isoforms are apoE E3 (Cys112/Arg158), E4 (Arg112/Arg158) and E2 (Cys112/Cys158). ApoE polymorphism is an essential determinant in the inter-individual variations of lipids in healthy subjects in various populations. Its influence can be significant on the efficacy of nutritional or therapeutic interventions. The allele APOE ε4 appears to be associated with oxidative stress, microglia activation, inflammation and increased risk of premature atherosclerosis. APOE polymorphism contributes to the lipid disorders in diabetes and obesity (Van Duijn *et al.* 1994).

Studies have shown that APOE genetics play a role in the extracellular deposition of amyloid, the hallmark of AD. Individuals afflicted with AD carrying the apoE4 isoforms have a greater number of Aâ plaques when compared to APOE ε3 carriers, and inheritance of an APOE ε4 allele increases the risk of AD when compared to APOE ε2 and APOE ε3 carriers (Carter 2005; Van Duijn *et al.* 1997; Gustaw-Rothenberg 2008; Gromadzka *et al.* 2005; Gromadzka *et al.* 2007). The general conclusion was that the APOE ε4 allele represents a major risk factor for AD in all ethnic groups studied, across all ages between 40 and 90 years, both men and women (Trembath *et al.* 2007). Moreover, carriers of APOE ε4 with mild cognitive impairment (MCI) remain at increased risk for dementia development (Gustaw-Rothenberg *et al.* 2010).

As far as estrogens are concerned, it is generally believed that cognitive postmenopausal decline may be related to their decreasing production. This generalization may be supported by substantial biologic evidence underlining the important influence of estrogen to cognitive functions (Pae *et al.* 2008; Manly *et al.* 2000; Sherwin 1998). Estrogen stimulates neurons and their ability to communicate with each other and may contribute to regulation of genes that influence neuron survival, differentiation, regeneration, and plasticity, especially in hippocampal structures closely related to cognition (McEwen 2002; Lam and Leranth 2003). Estrogen may protect nerve cells from excitotoxins (including amyloid beta) and may act as an antioxidant to shield nerve cells from oxidative damage thus protecting from neurodegeneration. There is still growing evidence suggesting that estrogens may influence neuropsychological functions in a mode which is closely related to APOE polymorphism.

Estradiol is linked to increased cellular production of apoE and consequently axonal growth (McAsey *et al.* 2006; Nathan *et al.* 2004). This effect was not observed, however, in a presence of protein coded by APOE ε4 or in neurons not exposed to apoE protein (Nathan *et al.* 2004).

Dementia development risk in women is significantly greater when APOE ε4 carriers are considered as opposed to the rest of feminine population studied (Bojar *et al.* 2012; Geerlings *et al.* 2001). Moreover, hormonal replacement therapy seems to be less effective in women carrying APOE ε4 alleles (Yaffe *et al.* 2000).

Nowadays there is a special clinical interest in pharmacogenetics, including variation of genes involved, substance metabolism with a particular emphasis on safety improvement. The wider use of pharmacogenetic testing is viewed by many as an outstanding opportunity to improve efficacy as well (Lazarou *et al.* 1998; Phillips *et al.* 2001; Weinshilboum 2003).

Considering all the data mentioned above, the study protocol was designed to determine the influence of hormonal therapy on cognitive functions of women in their postmenopausal stage of life in relation to APOE polymorphism.

METHODS

Patients

The patients were examined and data were collected in Institute of Rural Health in Lublin, Poland, in 2011.

Studied group was selected from the population of women from southern and eastern Poland. The inclusion criteria were: age 45–65, generally good health, education – at least completed primary school, minimum two years after the last menstruation period and FSH concentration over 30 U/ml. Exclusion criteria were: active cancer disease within the period of 5 years before recruitment, mental diseases (premenopausal depression included), pharmaceutical and alcohol addiction, disease with dementia symptoms. Additionally, Montreal Cognitive Assessment (MoCA) was used to check dementia signs and exclude potentially impaired patients (Magierska *et al.* 2008).

Finally 214 women aged 52–65 were recruited and examined. Gynecological history was obtained with a special attention to the estrogen plus progestogen constant therapy (EPT) for minimum 6 months after menopause.

Informed consent for participation in the study was obtained from the women. The study was approved by the Institutional Ethics Committee.

Neuropsychological assessment

CNS –Vital Signs computerized battery of tests (CNS Vital Signs, 1829 East Franklin Street, Bldg 500, Chapel Hill NC 27514, 919-933-0932) was used as a neuropsychological assessment tool (Gualtieri & Johnson 2006).

For the purpose of the study, the following CNS-VS tests/elements were applied: The Verbal Memory Test (VBM), Test of Motor Functioning – Finger Tapping Test (FTT), Symbol Digit Modalities Test (SDMT), Stroop Test (ST), Shifting Attention Test (SAT) and The Continuous Performance Test. The following cognitive functions were evaluated as domains: memory, verbal memory, visual memory, speed of processing, executive functions, psychomotor speed, reaction time, attention focusing and cognitive plasticity. Neurocognitive Index (NCI) was calculated on the basis of 5 domains: memory, psychomotor speed, reaction time, attention and cognitive plasticity. NCI and nine domains mentioned above were assessed based on the numbers corresponding with subject scores, standard scores and percentiles. These scores are categorized as: above average (percentile >74), average (percentile range 25–74), low average (percentile range 9–24), low (percentile range 2–8) and very low (percentile <2).

Genetic analysis

APOE polymorphism was examined in this study too. Genetic studies were performed in Unit of Molecular Biology of Department of Zoonoses in Institute of Rural Health in Lublin.

Genomic DNA isolation was extracted from 0.2 ml of human whole blood by QIAamp DNA Blood Mini Kit (Qiagen, USA) according to the producer's instructions.

Multiplex PCR was done according to Y.G. Yang *et al.* (2007) with some modifications. PCR reactions have been made in a single reaction tube with six primers including two common primers and two specific primers for each of two single nucleotide polymorphism (SNP) sites. The multiplex PCR reaction was done in 50 µl reaction volume which containing the following mix of reagents: 1.25 U *Taq* DNA polymerase (Qiagen, USA), 1× PCR buffer containing 15 mM $MgCl_2$ and 1× Q buffer (all from Qiagen, USA), 0.2 mM each of dNTP (Fermentas, Lithuania), 0.5 µM of each of six primers: FO, RO, FI-1, RI-1, FI-2, RI-2 (Eurogentec, Seraing, Belgium), nuclease-free water (Applied Biosystems, USA) and 5 µl of DNA. The reaction was performed in C1000 Thermal Cycler (BioRad) under the following conditions: initial denaturation at 95 °C for 5 min, then 35 cycles (denaturation 95 °C for 30 sec, annealing at 60 °C for 30 sec, elongation at 72 °C for 60 sec); final extension step at 72 °C for 7 min. The reaction products were detected in 2.5% agarose gels in the standard electrophoresis conditions. After ethidium bromide staining, the strips were read under UV light. The size of amplified DNA fragment with using two common outer primers (FO and RO) was 514 bp. Obtained DNA amplicons flanked by each of two sets of allele-specific inner primers (FI-1/RI-1 and FI-2/RI-2) showed different types of polymorphisms: 444 bp, 307 bp and 115 bp for ε3/ε4; 307 bp and 115 bp for ε3/ε3; 444 bp and 307 bp for ε4/ε4; 307 bp, 253 bp and 115 bo for ε2/ε3; 444 bp, 307 bp, 253 bp and 115 bp for ε2/ε4.

Statistical analysis

Two-way analysis of variance was used to calculate the significance of changes in NCI and the other nine cognitive domains in relation to APOE allelic polymorphism and EPT application. F statistics were used to test three different hypotheses: polymorphism effect on cognitive functions, EPT application effect on them, as well as the effect of interaction between APOE polymorphism and EPT application on cognitive functions. Scheffe's test was used in multiple testing of cognitive functions in relation to APOE polimorphisms. Due to small sample sizes of women with ε4/ε4 and women with ε3/ε4 they were combined together for statistical analysis. The *p*-value equal to 0.05 was considered significant. Statistical analysis was technically performed using STATISTICA software.

RESULTS

ε2/ε3 polymorphisms of APOE was found in 32 examined women which represented 14.95% of the sample, while ε3/ε3 polymorphisms of APOE occurred in 128 (59.81%), ε3/ε4 in 46 (21.49%) and ε4/ε4 in 8 (3.74%). The frequency of all types of APOE polymorphisms in studied sample appeared to be similar to their frequency in the general population.

106 examined women (49.5% of the whole sample) applied EPT constantly for minimum 6 months. EPT was applied in 18 women with ε2/ε3 polymorphisms

which represented 56.3% of this group, 68 women with ε3/ε3 (53.1%) and 54 (37.0%) with ε3/ε4 or ε4/ε4. EPT application did not differ significantly among 3 groups of APOE polymorphisms (χ^2=4.611, p=0.110).

Characteristics of the patients and their cognitive functions in the whole sample, in women with EPT and without EPT, as well as in women in three groups of polymorphisms were presented as means and 95% confidence intervals in Table 1. Table 2 includes statistical tests: two-way analysis of variance of cognitive functions in relation to EPT application and APOE polymorphisms, as well as Scheffe's test used in multiple testing of cognitive functions in relation to APOE polymorphisms.

Mean age of the patients was 56 years, their mean weight 69.0 kg and mean BMI 26.5 kg/m^2. Age, weight and BMI of examined women did not differ significantly in terms of APOE polymorphisms (p>0.05). However, weight and BMI were correlated to EPT application. Women taking EPT weighted significantly less (mean 66.4 kg) than women not applying EPT (71.5 kg). Consequently, women taking EPT had a significantly lower BMI (mean 25.4 kg/m^2) than women not applying EPT (27.3 kg/m^2). APOE polymorphisms correlated to the educational level (measured here by years in education). Women with APOE4 were significantly less educated than the others. EPT application did not correlated to the educational level.

The women after menopause have reduced NCI and cognitive functions, the mean scores were below 40 percentile. Average NCI was 25.7. The examined women obtained the worst scores in processing speed (mean 13.7), which corresponds with low average level. Better scores referred to cognitive flexibility, executive functioning, psychomotor speed and reaction time (means from 25 to 30 percentile). The patients achieved the best scores in general, verbal and visual memories, as well as in complex attention (means from 30 to 40 percentile, which corresponds with average level).

NCI and all studied cognitive functions of the patients depended significantly on APOE polymorphisms. NCI and four cognitive functions: executive functioning, psychomotor speed, complex attention and cognitive flexibility were the best for women with ε2/ε3, a little worse for women with ε3/ε3, and the worst for women with ε4. Three cognitive functions: memory, visual memory and processing speed were significantly worse for women with ε3/ε3 and ε4 than for women with ε2/ε3, while these cognitive functions in women with ε3/ε3 were not significantly different than in women with ε4. Reaction time stores were significantly worse for women with ε4 than for women with ε2/ε3 and ε3/ε3, while these cognitive function in women with ε2/ε3 were not significantly different than in women with ε3/ε3. Verbal memory scores were significantly worse for women with ε2/ε3 than for women with ε4,

Tab. 1. Patients' characteristics and cognitive domains' percentiles (means and 95% confidence intervals).

Variable	Total (n=214)	EPT		APOE		
		No (n=108)	Yes (n=106)	$\varepsilon_2/\varepsilon_3$ (n=32)	$\varepsilon_3/\varepsilon_3$ (n=128)	ε_4 (n=54)
Patients' characteristics						
Age (years)	56.6±0.4	56.5±0.6	56.7±0.8	56.8±1.2	56.6±0.6	56.6±0.8
Years in education	12.9±2.8	12.6±2.8	13.2±2.8	12.8±2.5	13.4±2.8	11.7±2.5
Height (cm)	161.6±0.8	161.7±1.2	161.5±1.2	160.1±1.4	162.2±1.0	160.9±1.2
Weight (kg)	69.0±2.1	71.5±2.4	66.4±1.6	67.9±4.4	68.8±1.8	70.0±3.6
BMI (kg/m^2)	26.4±0.6	27.3±0.8	25.4±0.6	26.4±1.4	26.2±0.6	26.9±1.2
Cognitive domains						
NCI	25.7±2.8	23.1±3.8	28.5±4.0	52.8±4.6	27.1±3.0	6.5±2.4
Memory	32.5±3.2	28.5±5.0	36.5±5.0	45.1±9.8	32.0±4.6	26±5.8
Verbal memory	36.9±4.2	30.9±6.0	43.0±5.6	47.2±10.2	37.5±5.6	29.3±7.2
Visual memory	37.7±3.4	36.4±4.8	39.1±5.0	50.9±8.2	36.1±4.4	33.8±7.0
Processing speed	13.7±2.2	12.4±2.6	15.1±3.4	28.4±7.0	12.6±2.2	7.7±3.4
Executive functioning	27.1±3.6	25.9±5.0	28.4±5.2	62.5±2.9	27.3±4.2	5.7±3.2
Psychomotor speed	27.4±3.2	26.8±4.8	27.9±4.2	46.2±7.4	28.2±3.8	14.3±5.0
Reaction time	29.4±3.2	26.9±4.6	31.9±4.6	37.6±6.6	32.3±2.2	17.5±5.8
Complex attention	33.4±4.0	30.6±5.6	36.2±5.6	71.8±5.2	34.9±4.4	7.1±3.6
Cognitive flexibility	26.3±3.6	24.5±4.8	28.1±5.2	62.6±5.4	26.2±4.0	4.9±2.6

EPT - estrogen plus progestogen therapy; APOE - apolipoprotein E gene

Tab. 2. Tests of two-way analysis of variance for patients' characteristics and cognitive domains' percentiles by EPT and APOE.

Variable	Tests of two-way analysis of variance						Multiple Scheffe's tests		
	EPT: No, Yes		APOE: ε2/ε3, ε3/ε3, ε4		Interaction (EPT * APOE)		ε2/ε3 vs ε3/ε3	ε2/ε3 vs ε4	ε3/ε3 vs ε4
	F	*p*-value	F	*p*-value	F	*p*-value	*p*-value	*p*-value	*p*-value
Patients' characteristics									
Age	0.004	0.836	0.070	0.932	0.040	0.960	0.951	0.931	0.991
Years in education	0.976	0.324	5.247	0.006	1.131	0.325	0.574	0.208	0.001
Height	0.100	0.803	2.400	0.096	0.600	0.554	0.174	0.804	0.389
Weight	8.599	0.004	0.071	0.932	0.316	0.729	0.923	0.716	0.816
BMI (kg/m^2)	11.467	0.001	0.184	0.832	0.551	0.577	0.952	0.857	0.519
Cognitive domains									
NCI	2.210	0.139	91.794	<0.001	1.205	0.302	<0.001	<0.001	<0.001
Memory	3.668	0.057	4.701	0.010	0.148	0.863	0.035	0.004	0.348
Verbal memory	4.073	0.045	3.144	0.045	0.995	0.372	0.272	0.032	0.250
Visual memory	0.556	0.457	4.917	0.008	2.359	0.097	0.012	0.010	0.845
Processing speed	9.030	0.003	19.452	<0.001	9.860	<0.001	<0.001	<0.001	0.102
Executive functioning	0.014	0.905	76.419	<0.001	1.684	0.188	<0.001	<0.001	<0.001
Psychomotor speed	0.079	0.778	22.026	<0.001	0.903	0.400	<0.001	<0.001	<0.001
Reaction time	1.544	0.215	7.842	<0.001	2.415	0.092	0.509	0.001	<0.001
Complex attention	0.837	0.361	89.676	<0.001	1.058	0.349	<0.001	<0.001	<0.001
Cognitive flexibility	0.358	0.550	87.576	<0.001	1.578	0.209	<0.001	<0.001	<0.001

EPT - estrogen plus progestogen therapy; APOE - apolipoprotein E gene

Tab. 3. Multiple Scheffe's tests of processing speed's percentiles by EPT and APOE.

APOE	EPT	n	M±95%CI	Group number	Group number					
					1	2	3	4	5	6
$\varepsilon_2/\varepsilon_3$	No	14	19.4±6.6	1	p	0.059	0.955	0.392	0.036	0.891
	Yes	18	35.3±10.1	2	0.059	p	<0.001	<0.001	<0.001	<0.001
$\varepsilon_3/\varepsilon_3$	No	60	15.2±3.7	3	0.955	<0.001	p	0.526	0.019	0.998
	Yes	68	10.3±2.6	4	0.392	<0.001	0.526	p	0.509	0.98
ε_4	No	34	4.4±2.8	5	0.036	<0.001	0.019	0.509	p	0.372
	Yes	20	13.3±7.3	6	0.891	<0.001	0.998	0.98	0.372	p

EPT - estrogen plus progestogen therapy; APOE - apolipoprotein E gene

while these cognitive function of women with ε2/ε3 were not significantly different than women with ε3/ε3, as well as these cognitive function in women with ε3/ε3 were not significantly different than in women with ε4.

Constantly using EPT for at least 6 months correlated with three cognitive functions: memory, verbal memory and processing speed, which were significantly worse for women taking EPT than for not taking ones.

The effect of interaction between APOE polymorphisms and EPT application was significant only in processing speed. EPT applying women with ε2/ε3 and ε4 obtained better scores in processing speed than women not taking EPT with these APOE polymorphisms. The opposite situation concerned women with ε3/ε3, women taking EPT achieved worse processing scores in comparison with women not taking it (Table 3, Figure 1).

DISCUSSION

The results of our study proved that there is an increased risk of cognitive impairment in postmenopausal women with APOE ε4. It is in agreement with previous studies and confirms their results (Pfeifer *et al.* 2002; Premkumar *et al.* 1996; Trembath *et al.* 2007; Drzezga *et al.* 2009).

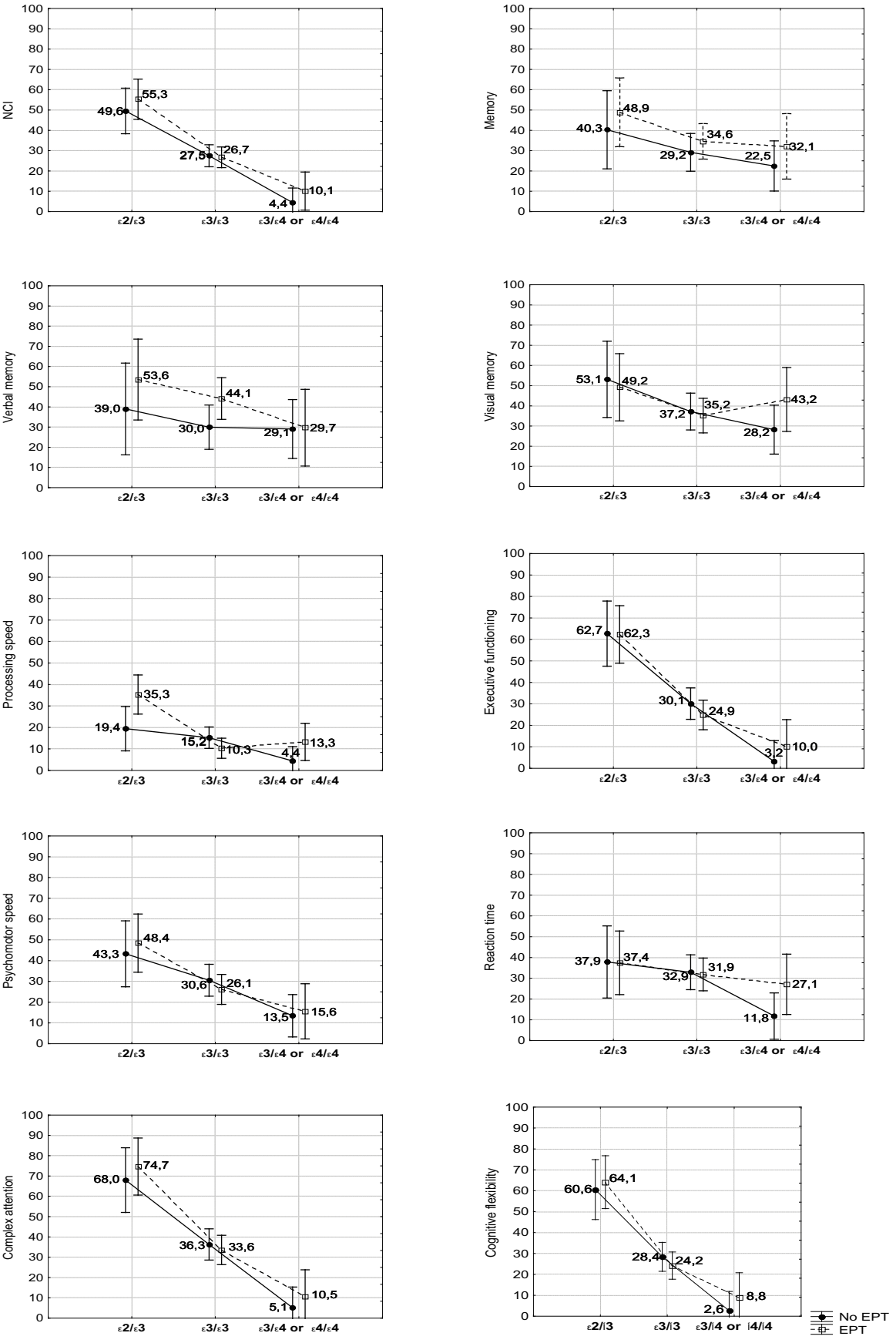

Fig. 1. Mean and 95% confidence intervals for NCI and cognitive functions' percentiles by interaction between APOE and EPT.

Particularly, patients with APOE ε4 were more impaired in cognitive domains connected with processing including: processing speed, executive functioning, psychomotor speed, reaction time, complex attention and cognitive flexibility than patients with other APOE polymorphisms. Moreover, protective effect of the presence of APOE ε2 may be suggested.

The link between the mechanism of estrogens neuroprotection and specific apoE proteins actions may appear to be of great importance in postmenopausal women. Procognitive effect of estrogens in relation to APOE polymorphism was first suggested in studies on mice models (Srivastava *et al.* 1996). The study performed by Payami *et al.* revealed that women with APOE ε4 were more susceptible to dementia development than men with the same polymorphisms (1996).

Our study proved that constant using of EPT correlated with three cognitive functions: memory, verbal memory and processing speed, which were significantly worse for women taking EPT than not taking ones. Interestingly, our study showed that the interaction between APOE polymorphisms and EPT application was significant only for processing speed. In this study women with allele ε2/ε3 and ε4 who were treated after menopause performed much better scores in processing speed parameter as compared with not treated (the ones who were not supplemented with hormones as the EPT). Interestingly, in allele ε3/ε3 carriers EPT didn't seem to significantly influence speed processing. Yue *et al.* (2007) supported the idea with imaging data. In his study spectroscopically measured hippocampal activity in ε4 carriers was much higher than in controls while exposed to HRT. However, women on HRT carrying APOE3 allele scored better on memory testing than apoE4 carriers. The benefit of HRT was than suggested in this particular study to allele ε3 carriers (Yue *et al.* 2007).

Cohort studies seemed to be less conclusive. Kand *et al.* (2004) based on the population sample of more than three thousand women had to conclude that little difference was found in mean of cognitive decline between current hormone users and never users. No significant interactions between hormone usage and APOE ε4 allele were observed (Kand *et al.* 2004).

On the other hand, the study by Burkhardt *et al.* (2004) involving a cohort of 181 healthy postmenopausal women (101 out of them on hormonal replacement therapy) reported the higher memory and learning functioning after implementing of estrogen replacement therapy in allele APOE4 non-carriers. Hence, once again, estrogens replacement therapy seemed to be much more beneficial in protecting memory in APOE4 non-carriers (Burkhardt *et al.* 2004).

Benefit of EPT in ε4 carriers which resulted from our study seems to be supported by others. Ryan *et al.* (2009) – similarly to us – reported that the dementia development risk of twice higher in ε4 carriers was significantly reduce by HTZ.

We seemed to found only a few pieces of the puzzle which is interplay of APOE, EPT effects and cognitive functioning in postmenopausal women.

The design of our study was consistent with a general idea of pharmacogenetics which refers to genetic differences in metabolic pathways, which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. Data mentioned above should be taken into consideration in deciding about potential benefits of EPT in postmenopausal women and to help to select the appropriate group for individualized treatment to potentiate benefit.

Cognitive functioning seems to be another interesting factor in this equation. Computerized batteries of tests and precise assessment of the cognitive profile in correlation to genetic makeup may give more data in predicting benefit of EPT in postmenopausal women.

CONCLUSION

The women after menopause have reduced NCI and cognitive functions. NCI and all studied cognitive functions of the patients depended significantly on APOE polymorphisms. The presence of APOE4 corresponded with decreased cognitive functions as opposed to APOE2 which was present in women with better level of cognitive functions.

Constant using of EPT correlated with three cognitive functions: memory, verbal memory and processing speed, which were significantly worse for women taking EPT than not taking ones.

The effect of interaction between APOE polymorphisms and EPT application was significant only in processing speed. EPT applying women with ε2/ε3 and ε4 obtained better scores in processing speed than women not taking EPT with these APOE polymorphisms. The opposite situation concerned women with ε3/ε3 – women taking EPT achieved worse processing speed scores in comparison with women not taking it.

It should be noted that APOE polymorphism assessment may be a factor in predicting the effect of EPT on cognitive functioning in postmenopausal period.

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