Cognitive functions, ApoE polymorphism and hormonal replacement therapy in postmenopausal women

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Introduction

Among the genetic markers of dementia, the ApoE gene has been widely examined because of its well-documented role in AD and vascular diseases. The three major isoforms are ApoE ε3 (Cys112/Arg158), ε4 (Arg112/Arg158) and ε2 (Cys112/Cys158). The allele ε4 appears to be associated with oxidative stress, microglia activation, inflammation and increased risk of premature atherosclerosis, contributes to the lipid disorders in diabetes and obesity as well as dementia (Carter 2005, Van Duijn et al 1994, Gustaw-Rothenberg et al 2010).

Growing body of evidence suggest that estrogenes may influence neuropsychological functions and modify the risk of developing dementia in a mode which is closely related to ApoE polymorphism (Burkhardt et al. 2004; Shuster et al 2010Payami et al 1996, Yue et al 2007, Kang et al 2004) Interestingly, estradiol is linked to increased cellular production of ApoE and consequently axonal growth (Nathan et al. 2004).
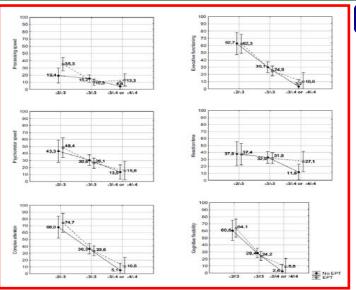
Risk of developing dementia in women is significantly greater when ApoE epsilon4 carriers are considered as opposed to the rest of feminine population studied (Geerling et al 2001). Moreover, hormonal replacement therapy was found to be less effective in women carrying ApoE ε4 alleles (Yaffe et al 2000)

Considering all the data the study protocol was designed:

Objectives/Aim

To determine the influence of estrogen plus ᐧ progesteron EPT therapy on cognitive functioning of women in their postmenopausal stage of life in relation to ApoE polymorphism.

Patients

The group of 214 healthy women was selected (106 women on EPT) for the final evaluation. Two years from the last menstruation as well as FSH level >30 U/ml and the lack of cognitive impairment on MoCA were considered the inclusion criteria.

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

Methods

Neuropsychological tests: CNS –Vital Signs computerized battery of tests was used (Gualtieri et al 2006). Cognitive domains were selected for assessment mainly: verbal memory, visual memory, executive functions, processing speed, psychomotor speed, reaction time, complex attention, cognitive flexibility. Scores were assess as PERCENTILES: above average (percentile > 74), average (percentile range 25-74), low average (percentile range 9-24), low (percentile range 2-8).

Genetic analysis: Genomic DNA isolation was extracted from 0,2 ml of human whole blood by QIAamp DNA Blood Mini Kit (Qiagen, USA). PCR was done according to Yang et al (2007).

Statistical analysis: Two-way analysis of variance was used to calculate the significance of changes in cognitive domains in relation to ApoE allelic polymorphism and the variable of EPT. F test was implemented to assess tree different hypotheses: lack of polymorphism effect, lack of the effect of EPT and in the end lack of the effect of combined polymorphism and therapy on cognitive functioning. ε4/ε4 and ε3/ε4 ere combined. P = 0.05 was considered significant. Statistical analysis was technically performed using STATISTICA software.

Results

Majority of women scored below 50 percentile on all the domains. Processing speed was scored below 25 percentile for ¾ of women .

ApoE polymorphism seemed to be important factor in majority of cognitive domains examined in examined population with exemption of Verbal and Visual memory. EPT effect was significantly noticeable in changing Processing speed

Processing speed, Executive functioning, Psychomotor speed, Reaction time, Complex attention and Cognitive flexibility presented significantly better in ε2/ε3 carriers an opposed to women with ε4 presence.

Women with ε3/ε3 genetics scored higher in Cognitive flexibility than their ε4-carriers counterparts. We didn't noticed however differences in the other cognitive domains assessed.

EPT seemed to improve functioning only in one domain - processing speed. E2/ε3 and ε4 carriers supplemented with hormones functioned significantly better in speed processing when compared to those non-treated. The opposite effect however was observed in ε3/ε3 carriers.

Conclusions

EPT seemed to improve functioning the domain of Processing speed in. E2/ε3 and ε4 carriers

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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