ORIGINAL ARTICLE

Polymorphisms of *apolipoprotein E* gene and cognitive functions of postmenopausal women, measured by battery of computer tests – Central Nervous System Vital Signs

Iwona Bojar [1], Angelina Wójcik-Fatla [1], Alfred Owoc [2], Andrzej Lewiński [3]

[1] Institute of Rural Health, Lublin, Poland; [2] College of Public Health, Zielona Góra, Poland; [3] Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital – Research Institute, Medical University of Lodz, Poland.

Correspondence to: Prof. Andrzej Lewiński, Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Polish Mother's Memorial Hospital – Research Institute, Rzgowska St. No. 281/289, 93-338 Lodz, Poland; TEL: +48 42 2711715; E-MAIL: alewin@csk.umed.lodz.pl

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Abstract

OBJECTIVES: *Apolipoprotein E* (*APOE*) gene belongs to the group of genes increasing the risk of the Alzheimer's disease (AD) development. The purpose of the study was the analysis of cognitive functions in postmenopausal women having different polymorphisms of *APOE* gene; battery of computer tests – Central Nervous System Vital Signs (CNS-VS) were employed. **METHODS:** The women were qualified into the examined group on the grounds of clinical symptoms (minimum 2 years after the last menstruation), as well as on the basis of FSH concentration. At the qualification stage, a short test – Montreal Scale of Cognitive Function Assessment (MoCA) was conducted. The assessment of cognitive functions was made with the use of diagnostic CNS-Vital Signs equipment. Genomic DNA isolation was extracted from human whole blood. Multiplex PCR reactions have been performed in a single reaction tube with six (6) primers, consisting of 2 common primers and 4 specific primers [2 – for each of 2 single nucleotide polymorphism (SNP) sites].
RESULTS AND CONCLUSIONS: About half of the examined postmenopausal women were placed below average in the majority of the examined cognitive functions. The biggest impairments occurred in the field of processing speed, and the smallest – in the field of verbal and visual memory. Polymorphisms of *APOE* gene were considerably linked with the level of results of the majority of cognitive functions among postmenopausal women, as measured by battery of computer tests – CNS-VS. The presence of *ε2/ε3* polymorphism of *APOE* gene impacted positively the obtained results of cognitive functions, whereas the presence of *ε3/ε4*, or *ε4/ε4* polymorphisms worsened the obtained results.

Introduction

It is estimated that Alzheimer's dementia in 15–40% may be hereditary conditioned. Point mutations in certain genes, i.e. *APP, PSEN1*, or *PSEN2,* inherited autosomally dominantly, are responsible for the family-related occurrence of that disease. This form often manifests early onset, i.e. prior to 65 year of age (Kalaria 2000). Most cases of Alzheimer's disease (AD) is a sporadic form (60–85%), with more complex hereditary type and multifactorial etiology. The genetic background of sporadic form of AD still remains unknown which impedes the development of modern diagnostics strategies, prophylaxis and AD

therapy based upon the individual genetic information examination (Kowalska 2009). *Apoliproprotein E* (*APOE*) gene, localised on chromosome 19, belongs to the genes increasing the risk of the disease development. Apoliproprotein E (apoE) is a polymorphic protein occurring in humans in 3 isomorphic forms: apoE2, apoE3 and apoE4, coded by 3 allelic sets of *APOE* gene: *ε2, ε3* and *ε4*. These (3) allelic sets are determined by the appearance of two (2) non-synonymous polymorphisms of single nucleotides (SNP) in exon 4 of *APOE* gene (Nyholt *et al* 2009; Mendel *et al* 2010).

In human population the most often occurring *APOE* gene allelic set is *ε3* (50–90%), *ε4* set of *APOE* gene meets frequency 5–15%, and *ε2* set of *APOE* gene – 1–15%. There are also mixed polymorphic forms (Mendel *et al* 2010).

Each apoE protein isoform differs in terms of functions. In the group of activities which could be related to the development of cognitive functions impairment as a consequence of AD, apoE is involved in the processes of oxidative damage, activation of microglia and of astrocytes, as well as in inflammation reaction. ApoE4 isoform protects neurons – however less actively – against the effects of oxidative stress, less effectively reduces the activation of microglia and astrocytes, and results in the intensification of inflammation reaction. It is more vulnerable to proteolytic digestion than apoE3 which leads to accumulation of reactive fragments of apoE4 in cytosol, to damage to the cytoskeleton and to degeneration of nervous tissue (Gromadzka *et al* 2005; Gromadzka *et al* 2007).

The presence of apoE4 also contributes to the accumulation of β-amyloid in the brain which – together with the described neurodegenerative changes – represents the risk factor of cognitive impairment and dementia (Trembath *et al* 2007). At the same time, the appearance of apoE2 isoform reduces the risk. The available data show that the person who fulfils the clinical, cognitive and etiological criteria of mild cognitive impairment (MCI) and is a carrier of *ε4* allele of *APOE* gene, is burdened with higher risk of impairment progression to dementia, caused by AD within few years than the person without such genetic feature (Premkumar *et al* 1996; Pfeifer *et al* 2002; Trembath *et al* 2007; Drzezga *et al* 2009).

The status of cognitive activities which can be observed between normal aging processes on one hand and dementia – on the other, is called – as mentioned above – MCI. Depending on the clinical image, several types of MCIs can be distinguished. If there is an impairment of only one (1) cognitive function, namely, memory, amnesic MCI is diagnosed, from which AD most often evolves. The annual conversion ratio of MCI into AD is often quoted in the range from 6 to 14% (Palmer *et al* 2003). There are also stable forms of MCI in which the intensification of cognitive impairment maintains on stable level – without progression or with very slow progression, as well as MCI cases in which after the lapse of some time, the improvement can be noted (reversible forms). Another distinction is the general MCI – with slightly impaired several cognitive functions, as well as the random MCI – with impaired single cognitive function but not memory. Mild cognitive impairments shall not be ignored since an increased risk of dementia has been shown by numerous authors practically in all the persons with MCI (Winbald *et al* 2004). In the epidemiological study of Kawas *et al* (2000), the authors determined the average conversion time from MCI into AD as equal to 4.4 years. The interest laid in MCI studies and in the earliest symptoms of cognitive functions impairment results from the evidence which shows that AD may cause changes inside the brain 10–20 years earlier than the first noticeable symptoms of the disease reveal.

On the basis of observations performed in premenopausal women, it may be concluded that in this group – most likely in the majority of the persons – reversible MCI occurs. It presumably results from a rapid decrease in estrogen production and the consequent lack of protective impact of these hormones on the central nervous system. For this reason the knowledge about epidemiology and conditions of MCI appearance, as well as of the risk of AD development in this group, seems to be necessary – in order to put this group under special prophylaxis.

The purpose of the study was the analysis of cognitive functions in the group of postmenopausal women having different polymorphisms of *APOE* gene; the battery of computer tests – CNS-VS was employed.

Methods

The study was conducted in the year 2010, in the Institute of Rural Medicine in Lublin, Poland. The group under examination was composed of women coming from southern and eastern Poland. The list of eligibility criteria included: age 50–65; good general condition of health; education – at least completed primary school. The criteria of exclusion from the study have been as follows: active cancer disease within the period of 5 years from recruiting, mental diseases in the interview, including depression in the premenopausal period, pharmacological and alcohol additions and/or diagnosed disease entity with dementia symptoms. The women were also qualified into that examined group on the grounds of clinical symptoms (minimum 2 years from the last menstruation), as well as on the basis of FSH concentration (FSH >30 mlU/ml). At the qualification stage, short test MoCA (Montreal Scale of Cognitive Function Assessment) was conducted – in order to include the woman patients who did not show dementia signs. MoCA test was designed as a fast screening tool used for the assessment of mild cognitive dysfunction (Magierska *et al* 2008). The maximum number of points in this test amounts to 30, and the score of 26 points or more is considered to be correct. All exam-

ined women who were qualified to further stages of the study, obtained more than 26 points in MoCA test; 107 postmenopausal woman patients were qualified. The age of the examined subjects ranged from 52 to 65 years, with the mean age 56.6±3.5 years.

The assessment of cognitive function was made with the use of diagnostic equipment CNS-Vital Signs (Polish version) (Gualtieri *et al* 2006), on the basis of software of CNS Vital Signs Company, of 1829 East Franklin Street, Bldg 500, Chapel Hill NC 27514, 919-933-0932. 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. The average standardized results were used for calculations, which enabled comparisons. CNS Vital Signs, on the basis of standard scores, qualifies the obtained results of a particular cognitive function into five (5) categories: more than average (more than 109 standard score points), average (90–109), below average (80–89), poor (70–79) and very poor (less than 70).

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 Yang *et al* (2007), with some modifications. PCR reactions have been made in a single reaction tube with 6 primers, consisting of 2 common primers and 4 specific primers (2 – for each of 2 SNP sites). The multiplex PCR reaction was done in 50 µl reaction volume which containing the following mix of reagents: 1,25U *Taq* DNA polymerase (Qiagen, USA), 1x PCR buffer containing 15 mM $MgCl_2$ and 1x 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 bp for *ε2/ε3;* 444 bp, 307 bp, 253 bp and 115 bp for *ε2/ε4.*

Ten (10) cognitive functions of the examined women were analysed in accordance with 4 groups of *APOE* polymorphism. Due to significant differences in the population of those 4 groups, a non-parametric analysis of variance – Kruskal-Wallis' F-test was used. The analysis also included a comparison of nine (9) cognitive functions in all examined women and – separately – among women in each polymorphic group, using the Friedman's test. The level of significance – $p<0.05$ was accepted. Statistical analyses were performed with STATISTICA software. Average standard scores were given as medians. Results of assessments of cognitive functions of women in each polymorphic group were given as percentages.

Results

The examined women had NCI on low average level, i.e., 89.0 points. Nine (9) cognitive functions (with exclusion of NCI) differed considerably from one another (χ^2=99.173; p=0.000) (***Table 1***). The biggest impairments among the examined women occurred in the processing speed (average – 78.0 points which means low level). The women, when examined in terms of executive functioning and cognitive flexibility, performed a bit better (average – 89.0), which corresponds with low average level. Then, in the next round, the women – examined in the field of psychomotor speed and complex attention – had better results (average – 90.0), and the best results in terms of verbal memory (average – 93.0) and visual memory (average 94.0), which corresponded with the average level (***Table 2***).

As regards genetic background, *ε2/ε3* polymorphism of *APOE* gene occurred in 16 examined women, which represented 14.95% of the sample, while *ε3/ε3* polymorphism was found in 64 (59.81%), *ε3/ε4* – in 3 (21.49%), *ε4/ε4* in 4 (3.74%) of the examined women. The above four (4) groups of women, distinguished on the basis of polymorphisms, did not differ significantly in terms of age (H=0.427; p=0.935).

The presence of particular *APOE* gene polymorphisms among the women included in the study, was essentially related to all the cognitive functions, except for verbal memory (***Figure 1***).

NCI value differed considerably among four (4) *APOE* gene polymorphic groups (H=54.851; p=0.000). The considerably better NCI was obtained by women with *ε2/ε3* and *ε3/ε3* polymorphisms, significantly poorer – with *ε3/ε4* and the poorest one – with *ε4/ε4.*

Memory differed considerably between four *APOE* polymorphic groups (H=9.548; p=0.023). Women with *APOE ε2/ε3* polymorphism had considerably better memory than women with *ε3/ε3* and *ε3/ε4* polymor-

Tab. 1. Assessment of cognitive functions in particular groups of *APOE* gene polymorphisms (in %).

Domain	Category	*ε2/ε3*	*ε3/ε3*	*ε3/ε4*	*ε4/ε4*	Total
NCI	Above	0.00	0.00	0.00	0.00	0.00
	Average	100.00	53.13	13.04	0.00	49.53
	Low Average	0.00	26.56	13.04	0.00	18.69
	Low	0.00	17.19	30.43	25.00	17.76
	Very Low	0.00	3.13	43.48	75.00	14.02
Memory	Above	18.75	9.38	4.35	0.00	9.35
	Average	50.00	37.50	43.48	0.00	39.25
	Low Average	18.75	25.00	39.13	25.00	27.10
	Low	12.50	17.19	4.35	25.00	14.02
	Very Low	0.00	10.94	8.70	50.00	10.28
Verbal memory	Above	18.75	17.19	8.70	0.00	14.95
	Average	56.25	39.06	43.48	25.00	42.06
	Low Average	6.25	9.38	26.09	0.00	12.15
	Low	0.00	21.88	17.39	50.00	18.69
	Very Low	18.75	12.50	4.35	25.00	12.15
Visual memory	Above	6.25	4.69	8.70	0.00	5.61
	Average	75.00	56.25	52.17	0.00	56.07
	Low Average	18.75	25.00	30.43	75.00	27.10
	Low	0.00	6.25	4.35	25.00	5.61
	Very Low	0.00	7.81	4.35	0.00	5.61
Processing speed	Above	6.25	0.00	0.00	0.00	0.93
	Average	50.00	18.75	13.04	0.00	21.50
	Low Average	31.25	29.69	13.04	0.00	25.23
	Low	6.25	32.81	34.78	0.00	28.04
	Very Low	6.25	18.75	39.13	100.00	24.30
Executive functioning	Above	25.00	3.13	0.00	0.00	5.61
	Average	75.00	40.63	13.04	0.00	38.32
	Low Average	0.00	26.56	4.35	0.00	16.82
	Low	0.00	17.19	4.35	0.00	11.21
	Very Low	0.00	12.50	78.26	100.00	28.04
Psychomotor speed	Above	12.50	3.13	4.35	0.00	4.67
	Average	75.00	48.44	26.09	25.00	46.73
	Low Average	12.50	23.44	17.39	25.00	20.56
	Low	0.00	15.63	26.09	0.00	14.95
	Very Low	0.00	9.38	26.09	50.00	13.08
Reaction time	Above	0.00	1.56	0.00	0.00	0.93
	Average	68.75	53.13	30.43	0.00	48.60
	Low Average	25.00	21.88	30.43	0.00	23.36
	Low	6.25	10.94	17.39	25.00	12.15
	Very Low	0.00	12.50	21.74	75.00	14.95
Complex attention	Above	50.00	4.69	0.00	0.00	10.28
	Average	43.75	51.56	13.04	0.00	40.19
	Low Average	0.00	23.44	13.04	0.00	16.82
	Low	0.00	18.75	4.35	25.00	13.08
	Very Low	6.25	1.56	69.57	75.00	19.63
Cognitive flexibility	Above	18.75	1.56	0.00	0.00	3.74
	Average	81.25	42.19	8.70	0.00	39.25
	Low Average	0.00	23.44	8.70	0.00	15.89
	Low	0.00	21.88	4.35	25.00	14.95
	Very Low	0.00	10.94	78.26	75.00	26.17

ε2/ε3 - ε2/ε3 polymorphism of *APOE* gene; *ε3/ε3 - ε3/ε3* polymorphism of *APOE* gene; *ε3/ε4 - ε3/ε4* polymorphism of *APOE* gene; *ε4/ε4 - ε4/ε4* polymorphism of *APOE* gene

Tab. 2. Analysis of cognitive functions in particular groups in *APOE* gene polymorphisms.

Domain	*ε2/ε3*			*ε3/ε3*			*ε3/ε4*			*ε4/ε4*			Total			H	*p*-value
	Min–Max	M±SD	Me	Min–Max	M±SD	Me	Min–Max	M±SD	Me	Min–Max	M±SD	Me	Min–Max	M±SD	Me		
NCI	92.0–108.0	101.1±5.3	102.0	64.0–105.0	89.1±9.3	90.5	54.0–92.0	72.3±11.3	72.0	29.0–78.0	53.5±20.5	53.5	29.0–108.0	85.9±14.6	89.0	54.851	0.0000
Memory	79.0–116.0	97.6±12.4	96.0	44.0–118.0	89.1±15.8	88.5	54.0–110.0	89.2±12.9	89.0	65.0–87.0	73.0±9.7	70.0	44.0–118.0	89.8±15.1	89.0	9.548	0.0228
Verbal memory	61.0–118.0	96.1±18.0	101.0	42.0–125.0	91.0±19.1	93.0	46.0–115.0	89.7±15.9	90.0	57.0–96.0	75.3±16.0	74.0	42.0–125.0	90.9±18.4	93.0	4.579	0.2050
Visual memory	84.0–119.0	100.1±10.2	101.0	50.0–122.0	92.1±14.3	93.5	62.0–116.0	93.7±13.0	90.0	78.0–84.0	91.8±2.9	82.5	50.0–122.0	93.3±13.6	94.0	9.508	0.0232
Processing speed	61.0–111.0	89.1±11.8	90.5	40.0–106.0	78.2±12.4	78.5	26.0–101.0	71.8±15.7	71.0	52.0–68.0	59.3±8.5	58.5	26.0–111.0	77.7±14.5	78.0	22.566	0.0000
Executive functioning	91.0–117.0	105.1±6.8	106.0	58.0–111.0	87.2±14.0	88.0	19.0–100.0	55.3±22.3	54.0	40.0–69.0	48.5±13.8	42.5	19.0–117.0	81.6±22.9	87.0	54.816	0.0000
Psychomotor speed	87.0–111.0	98.4±8.4	97.5	60.0–115.0	88.4±12.7	90.0	51.0–116.0	79.2±13.8	78.0	47.0–94.0	71.3±20.3	72.0	47.0–116.0	87.3±14.1	90.0	22.211	0.0001
Reaction time	74.0–109.0	94.3±9.0	95.0	36.0–121.0	89.2±16.0	91.0	50.0–109.0	81.9±15.3	82.0	48.0–79.0	61.0±13.0	58.5	36.0–121.0	87.3±16.1	89.0	15.078	0.0018
Complex attention	18.0–118.0	103.1±23.6	109.5	67.0–115.0	92.0±12.5	92.0	16.0–99.0	58.0±24.8	54.0	29.0–73.0	47.0±19.7	43.0	16.0–118.0	84.7±24.5	90.0	49.843	0.0000
Cognitive flexibility	92.0–115.0	105.1±6.4	106.0	60.0–112.0	86.6±13.6	88.0	18.0–96.0	54.3±21.9	53.0	18.0–70.0	41.8±21.4	39.5	18.0–115.0	80.8±23.4	87.0	57.797	0.0000

Min – Minimum; Max – Maximum; M – Mean; SD – Standard Deviation; Me – Median; *ε2/ε3 - ε2/ε3* polymorphism of *APOE* gene; *ε3/ε3 - ε3/ε3* polymorphism of *APOE* gene; *ε3/ε4 - ε3/ε4* polymorphism of *APOE* gene; *ε4/ε4 - ε4/ε4* polymorphism of *APOE* gene; H – Kruskal-Wallis test; *p*-value (level of significance)

phisms of *APOE* gene. Women with allele *ε3/ε3* or *ε3/ε4* had considerably better memory than women with *ε4/ε4*.

Verbal memory did not differ considerably among 4 groups of examined *APOE* gene polymorphisms (H=4.579; *p*=0.205).

Visual memory differed significantly among 4 examined *APOE* gene polymorphisms (H=9.508; *p*=0.023). Women with APOE *ε2/ε3* had indeed better visual memory than women with other allele (*ε3/ε3, ε3/ε4, ε4/ε4*).

Four (4) *APOE* polymorphic groups had a considerable impact also on other cognitive functions, i.e., processing speed (H=22.566; *p*=0.000), executive functioning (H=54.816; *p*=0.000), psychomotor speed (H=22.211; *p*=0.000), reaction time (H=15.078; *p*=0.002), complex attention (H=49.843; *p*=0.000) and cognitive flexibility (H=57.797; *p*=0.000).

Much better results in the field of processing speed, executive functioning, psychomotor speed, complex attention

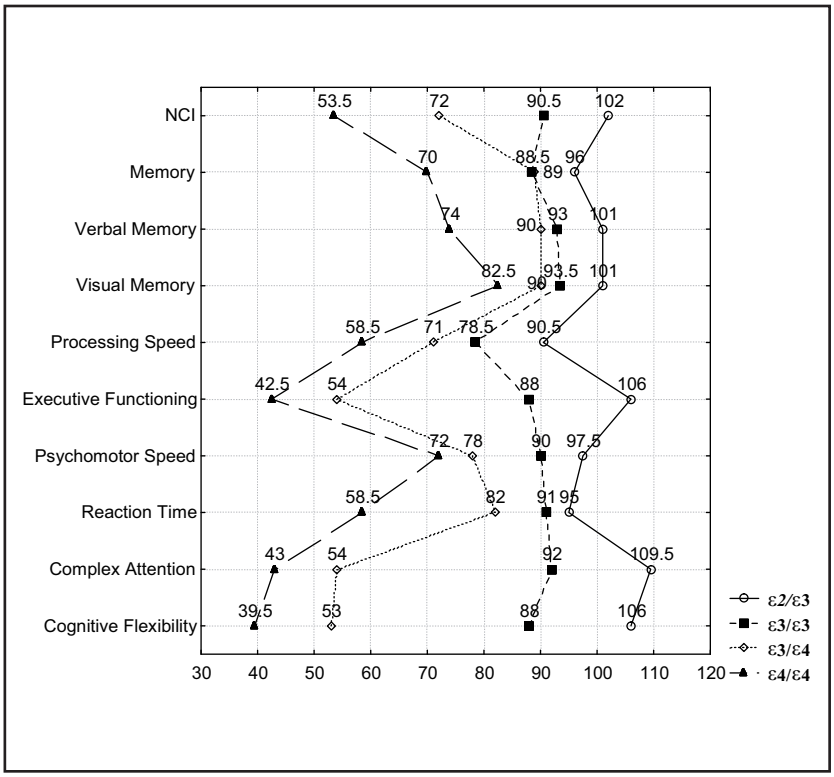

Fig. 1. Average standard scores for cognitive functions in particular groups of *APOE* gene polymorphisms.

and cognitive flexibility were exposed by women with *ε2/ε3* polymorphism, considerably weaker enumerated functions – with *ε3/ε3* polymorphism, and the poorest – with *ε3/ε4* and *ε4/ε4* polymorphisms. Undoubtedly, the shortest reaction time was characteristic for women with *ε2/ε3* and *ε3/ε3* polymorphisms, much longer – for the examined subjects with *ε3/ε4*, and the longest – with *ε4/ε4*.

Table 1 presents the distribution of cognitive functions, with the break-down into following categories: above, average, low average, low and very low depending on particular *APOE* polymorphisms (in percentages). All women with *ε4/ε4* had a very low NCI, processing speed and executive functioning, as well as low or very low verbal memory, reaction time, complex attention and cognitive flexibility. All women from *ε2/ε3* had average NCI and average, or above average executive functioning, complex attention and cognitive flexibility. Women with *ε3/ε3* and *ε3/ε4* polymorphisms had worse results than women with *ε2/ε3* but better than women with *ε4/ε4*.

Nine (9) cognitive functions (except for NCI) differed considerably from each other in the group of women with *ε2/ε3* (χ^2=34.090; p=0.000), *ε3/ε3* (χ^2=67.195; p=0.000), *ε3/ε4* (χ^2=78.416; p=0.000) and *ε4/ε4* (χ^2=23.297; p=0.003) polymorphisms. In the group of women with *ε2/ε3* polymorphism, the worst results were exhibited by the examined subjects in the proceeding speed, reaction time, memory and psychomotor speed, as compared to other cognitive functions among those women. In the group of women with *ε3/ε3* polymorphism, considerably worse was with the proceeding speed as compared to other cognitive functions among those women. In the group of women with *ε3/ε4* and *ε4/ε4* polymorphisms, the worst results were among the group of the examined women in the field of cognitive flexibility, complex attention and executive functioning as compared with other cognitive functions of those women (***Figure 1***).

Discussion

The postmenopausal decrease of estrogen concentration explains the cognitive and psychic impairments observed in that period. Both clinical studies and preclinical research provide data indicating the protective role of estrogens for the cognitive functioning (Manly *et al* 2000; Sherwin 1998), and the protective function of estrogens in the examined neurotoxicity models, including the neurotoxicity related to amyloid beta (Aβ), as well (Petanceska *et al* 2000). A lot of research indicate also the contribution of estrogens in neuronal plasticity, particularly in hippocampus structures, in connection with *APOE* gene polymorphism (Lam *et al* 2003; McEwen 2002). Estradiol enhances the production of apoE (McAsey 2006). It also causes the acceleration of the nerve growth processes. These dependencies suggest the important regulatory role of estradiol in neuronal growth regulation in the absence of apoE, or in the presence of apoE4 isoform (Nathan *et al* 2004). Constant administration of estradiol halts the activation of glia and lowers the expression of apoE, which is important for neuroplasticity. The examination of *APOE* gene polymorphism may be essential for the assessment of risk of certain neurological diseases, such as AD, or Parkinson's disease, which considerably escalates in postmenopausal period (de Stefano *et al* 2004; Ghebremedhin *et al* 2006).

It was confirmed in our study that of *APOE* gene polymorphism was significantly linked with the level of majority of cognitive functions among postmenopausal women, as measured by the battery of computer tests – CNS-VS, except for verbal memory. The presence *ε2/ε3* polymorphism of *APOE* gene placed the results obtained by the examined persons in average and above average ranges. The presence of *ε4* allele of *APOE* gene in heterozygous set (*ε3/ε4*) deteriorated the obtained results, the lowest results (within the poor and very poor range) were found among women having homozygous set *ε4/ε4 APOE*.

Similar dependencies between the cognitive functions were obtained in the study by Blair *et al* (2005) embracing big group of 6202 people of Caucasian race, among whom the positive change of the results of cognitive functions were observed, ranging from persons with *ε4/ε4* polymorphism to persons having *ε2* allele. In the same study, it was observed that among Afro-Americans the similar dependency was confirmed with regard to the psychomotor speed. On the basis of that study – conducted among middle-aged persons – the conclusion was drawn that the processes in which *APOE* genotype is an intermediary, the increasing risk of dementia, function a way ahead of clinically open dementia (Blair *et al* 2005).

The advanced age and the genetic background are considered to be the most powerful risks of dementia development (Blennow *et al* 2006; Morris *et al* 2010). A lot of studies show the negative impact of *ε4* of *APOE* gene as the main genetic factor of the vulnerability on later dementia (Farrer *et al* 1997; Bertram *et al* 2008). Other isoforms have neutral impact (apoE3) or even protective (apoE2) on neurodegeneration changes of the brain (Corder *et al* 1994; Talbot *et al* 1994). However, it turnes out in other studies that the accumulation of amyloid β in the brain starts at the middle-age and escalates with the advancement of age (Morris *et al* 2010).

It has been confirmed by other authors that the possessing of *ε4* allele of *APOE* gene, which is a risk factor for dementia-related diseases at older age, does not affect the results among people – without symptoms under examination – in the preclinical dementia period (Bunce *et al* 2004).

At present, there is drive for drafting recommendations in order to prevent, or delay the occurrence of the dementia symptoms. Therefore, it is necessary to identify and treat people in preclinical stages of disease, such as MCIs. Data from clinical studies show the positive effects of applying cholinesterase among patients with MCIs (Salloway *et al* 2004). Taking into account that the disease process may start several years prior to the beginning of observing cognitive problems (Small *et*

al 2002), the detection of the increased risk in as early period as possible may bring new possibilities in treatment and prophylaxis. Unfortunately, currently there is not method of nonsymptomatic identification of adults in which the later stage of AD will develop. The combination of genetic, neuropsychological and neuroimage strategies may seem practical within such scope. *APOE* gene – as a vulnerability gene – most visibly related to the later AD, with the presence of one *ε4* allele of *APOE* gene, doubles the risk of AD and with two alleles – causes fivefold increase of risk growth (Mayeux 2003).

Bearing in mind the pathomechanism which is related to the role of apoE in the processes of production and clearance of amyloid β and also – in consequence – the repairs of synapses and neurons, as well as linking of that role with the impact of estrogens, both on central nervous system and apoE metabolism, the group of women directly after postmenopausal period should be taken into account as particularly exposed to the occurrence of cognitive impairments. The reflection of this thesis are data collected by us in this study, where more than half of the examined women have obtained the results below the average and lower.

The examined women had the worst results in terms of processing speed which are the first changes related to age. The examination of the postmenopausal cognitive functions call for further search of the relations between sex hormones and genomic factors, also due to the fact that many studies challenge the leading role of estrogens in preserving cognitive functions.

The studies can also be found reporting that the activity of the brain, observed by functional magnetic resonance (MRI) in the field of working memory during stimulation, has been higher among persons having *ε3/ε4* polymorphism of *APOE* gene rather than among those having *ε3/ε3* polymorphism of gene in question (Wishart *et al* 2006).

Despite the fact that polymorphism for *APOE* at the stage of current research is not specific enough, it may be a very important completion of classifying premenopausal and postmenopausal woman patients into the group with transitional form of MCI where prophylaxis is very important, as well as into the group where the cognitive impairments are first symptoms of the developed dementia and call for treatment.

Summing up our results, it should be stressed that about half of postmenopausal examined women was placed in the majority of the examined cognitive functions below average. The biggest impairments occurred in the field of processing speed, and the smallest – in the field of verbal and visual memory. Polymorphism of *APOE* gene was considerably linked with the level of the majority of cognitive functions among postmenopausal women measured by battery of computer tests – CNS-VS. The presence of *ε2/ε3* polymorphism of *APOE* gene impacted positively cognitive functions, whereas the presence of *ε3/ε4*, or *ε4/ε4* polymorphisms worsened the functions in question.

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