An analysis of the relationship between the polymorphism of certain genes in candidates for cognitive impairments against cognitive functions in female white-collar workers

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Abstract

Introduction: The aim of this study was to assess correlation between the apolipoprotein E gene polymorphism (APOE) and estrogen receptor α (ERα) and cognitive functions in women.

Material and methods: A group of 300 women was recruited to the study. The inclusion criteria were: age (45-60) and intellectual work. The computerized battery of the Central Nervous System Vital Signs test was used to diagnose cognitive functions. Authors used genotyping based on detecting differences in the sequences of nucleotides of the APOE allele genes, as well as estrogen receptors or DBH (single nucleotide polymorphism, SNP). For both the polymerase chain reaction (T-ARMS PCR) and multiplex PCR (T-ARMS PCR) the primers for alleles were used.

Key words:

cognitive functions, Apolipoprotein E, estrogen receptor α

Results: No correlation was found between the cognitive functions and presence of genotypes $\varepsilon_2/\varepsilon_3$ and $\varepsilon_3/\varepsilon_3$ APOE polymorphism. Analyzing the relation between XbaI polymorphism and ERα PvuII and cognitive functions only the correlation between reaction time and presence of both types of estrogen α receptor polymorphism was noticed. Best grades for reaction time were reported in women with AA genotypes and TT, lower grades were given for women with AG genotypes and TC, while the lowest grades for this cognitive function were received by women with GG genotypes and CC.
Conclusions: Due to the huge discrepancies between authors regarding the influence of estradiol concentration and its expression in the central nervous system, as well as the ER α Xba1 and PvuII genes and APOE gene polymorphism over cognitive functions, there is a need for further research in the subject.

Introduction

Cognitive impairments are one of the biggest challenges to contemporary medicine, both due to the fact that they are becoming increasingly widespread in the society and due to their serious health, social and economic consequences. Findings of numerous studies on the impairment epidemiology are ambiguous, due to various difficulties related to impairment diagnosing. Since there are neither certain biological markers of the condition nor reputable research, the diagnosis becomes certain only when the impairment disorders are truly severe.

The most usually reported indicators of cognitive disorders suggest that the condition affects around 1.5% of the whole population [1]. The symptoms of these impairments increase with age, which means that the older the patients, the higher the prevalence. An analysis of various age groups in five-year intervals show that the prevalence rate doubles, up to 30% among individuals over 85 [2].

The probability of diagnosing cognitive disorders is low in cases of low intensity, which means the times when there is still a chance to affect the factors influencing the condition. Recognizing the most probable cause of these impairments - the Alzheimer's disease - is rarely a serious challenge. In case of mild cognitive disorders that hardly affect daily life (unlike degenerative diseases) the diagnosis is much more of a challenge [3]. Medical negligence can be partly due to the concept that the cognitive disorders are bound to happen after reaching a certain age and that there are some factors of vascular origin that are hard to modify. Yet, there is a huge gap between the natural aging that usually deteriorates one's mental capabilities and dementia. This is why it is so important to perform detailed medical examination of the patient, including some extra examination, even if there is little complaint about the cognitive impairment. Since mild cognitive impairment often affect professionally active individuals, including white-collar workers, failure to recognize them can have various health, as well as social and economic consequences [4]. Apart from assessing the severity of cognitive impairment and determination of deficits specific for an individual, there is also an analysis of the individual factors, affecting the risk of deterioration, that can partly be modified. Among the factors increasing the risk of cognitive impairment there are: age, hypertension or hypercholesterolaemia in midlife, as well as tobacco smoking, head injuries or late-life depression [5]. The epidemiological research shows that the female sex is an independent risk factor and women are more prone to suffer from cognitive disorders, both mild and dementia, caused by Alzheimer's disease [6].

Progress in molecular biology has led to discovery of genes and related biochemical pathways increasing the risk of certain conditions leading to dementia. It was reported that most cases of cognitive disorders are not inherited but they are rather determined by genes [7]. In case of the Alzheimer's disease, presence of even one e4 allel in the apolipoprotein E is an important risk factor [8]. Apart from the APOE polymorphism there is also the CYP46 gene polymorphism, as well as SORL1 [9,10]. Numerous causative mutations in the genes coding proteins have been

noticed: beta amyloid precursor, presenilin 1 and presenilin 2 [11]. Thanks to these discoveries, targeted therapy based on monoclonal antibodies has been introduced into clinical research [12]. Furthermore, the genetic component for other types of cognitive disorders were discovered – like Lewy's dementia or frontotemporal dementia [13,14].

The gene polymorphism for APOE is the only factor causing the sporadic Alzheimer's disease, which is why it is often mentioned while discussing the genetic determination of other genetic disorders, including those of mild severity. The APOE gene is located on the 19th chromosome (19q13.31) and its polymorphism means there are 6 variants of the gene: 3 homozygotic (e2/e2; e3/e3; e4/e4) and 3 heterozygotic (e2/e3; e2/24; e3/e4) [15]. In the general population, the presence of certain alleles is determined as follows: e3 – 75%, e4 – 15%, e2 – 8%. [15]. Research shows that even one e4 allele increases the risk of the Alzheimer's disease and the e2 allele decreases the risk of cognitive impairments [16,17]. The APOE gene produces proteins that differ depending on their polymorphism. The differences mainly include the presence of amino acids of arginine and cysteine in the 112 and 158 position. In the central nervous system, APOE is responsible for transport and metabolism of lipids. This protein is mostly expressed in astrocytes and microglia [18]. The most recognized hypothesis for the AD pathogenesis is the amyloid cascade theory.

Depending on the isoform, APOE partakes in protein degradation or creates insoluble complexes destroying nervous cells. The role of APOE polymorphism in other cognitive dysfunctions that may also be caused by either death or incorrect functioning of cells and structures of the nervous and limbic systems is a subject of ongoing research [19].

The presence of estrogen receptors in processes of thinking and memorizing the brain's resources suggests that they affect the cognitive functions [20]. Numerous research studies have shown that estrogen hugely affect the work of the central nervous system [21]. They have a protective role against neurotoxic factors, as well as the production of oligomeric forms of the A-beta peptide, as well as tau protein aggregation and other processes related to AD pathogenesis [22,23]. In addition, estrogen participate in synaptogenesis, induce the production of growth factors, protect against oxidative stress and participate in neuronal plasticity of the limbic system structures, including the hippocampus considered as the place of producing, modifying and reproducing engrams [24-27]. The huge influence of estrogen over neurotransfer, including acetylocholine synthesis, noadrenaline, dopamine and serotonine concentration [28-31]. All the above-mentioned factors play a key role in the learning, memorizing and emotion control processes. Lack of estrogen causes a suppression of the cholinergic system, the dysfunction of which is characteristic for AD. Apparently, the cognitive impairment is not necessarily caused by lowering of estrogen levels in the blood or decrease in the number of their receptors within the nervous system, as this affects all women in the postmenopausal period. Various authors are pointing to the role of estrogen receptors in various pathological processes happening in women, including the central nervous system disorders [32-34].

Estrogens work through 2 independent steroid receptors – ER alfa i ER beta. The genes responsible for coding the proteins creating the receptor's structure are located on the long arm of chromosome 6 (6q24-27) and the long arm of chromosome 14. The genes coding ERα have different polymorphic variants. One of the most analyzed are two polymorphisms of the SNP type – XbaI and PvuII. The XbaI polymorphism is located in the intron of gene 1 ERα. It is produced by the A/G transition and called IVS1-351 [35]. Polymorphism PvuII is known as IVS1-397T/C and it is caused by T/C transition in intron 1 [36]. There is no uniform opinion about the influence of alpha gene's polymorphism over the cognitive functions in women.

Aim

The authors aimed at an analysis of the relationship between the apolipoprotein E gene polymorphism (APOE) and estrogen receptor α (ERα) with cognitive functions in women having white-collar jobs.

Methodology

Study group

300 women working at different institutions in the Lublin region were subjects of the study. The inclusion criteria were: age (45-60) and intellectual work. Blood tests were taken to assess the concentration of FSH and to isolate DNA.

The participants were divided into three groups, according to their reproductive status:

- women in early perimenopausal period: menstruating with FSH lower than 20 mlU/ml;
- women in late perimenopausal period: menstruating with FSH of 20 mlU/ml and more;
- women in the postmenopausal period - not menstruating for at least 12 months.

Assessment of cognitive functions

The assessment of cognitive functions was conducted using technologies, based on behavioural and neurocognitive software – CNS Vital Signs (Polish version), by CNS Vital Signs, 1829 East Franklin Street, Bldg 500, Chapel Hill NC 27514, 919-933-0932. The presented cognitive functions were: Composite Memory, Verbal Memory, Visual Memory, Psychomotor Speed, Reaction Time, Complex Attention, Cognitive Flexibility, Processing Speed, Executive Function, Simple Attention, Motor Speed.

For the analysis, standard scores derived from CNS VS tests were used. Clinical report based on the CNS Vital Signs examination divides the women into 5 groups, according to the Neurocognitive Index (NCI) and 11 cognitive functions. Standard scores allow to classify the examination as: above average (>109), average (90-109), low average (80-89), low (70-79), very low (<70). The CNS VS report gives the value of Neurocognitive Index which is calculated digitally, basing on five domains: memory, psychomotor speed, reaction time, attention and cognitive flexibility.

DNA isolation, estrogen receptor α and Apolipoprotein E polymorphisms

The genome DNA was extracted from blood, using Qiagen (commercially available sets for DNA extraction). The amount and purity of the extracted material was measured using NanoDrop spectrophotometer. Authors used genotyping based on detecting differences in the sequences of nucleotides of the APOE allele genes, as well as estrogen receptors or DBH (single nucleotide polymorphism, SNP). For both the polymerase chain reaction (T-ARMS PCR) and multiplex PCR (T-ARMS PCR) the primers for alleles were used. Amplification products were detected in agarose gels after electrophoresis. To confirm the findings a PCR-RFLP reaction was conducted, where the amplification product has been influenced by restrictive enzyme *Hha*I and digestion products were visualised on polyacrylamid gels after electrophoresis, after which a restrictive pattern characteristic for every genotype was identified. In addition, the Allele Specific PCR (ASPC reaction) was conducted, using specific primers in which amplification products have undergone electrophoresis and the results of genotyping compared to the results obtained through other methods. The amplification products were sequenced and the patterns were compared against the data from the Gene Bank.

Statistical analysis

The data were statistically analyzed using STATISTICA software. We estimated mean values (M) with standard deviations (SD) for continuous variables, and absolute (n) and relative numbers (%) of occurrence of items for categorical variables.

The test F analysis of variance was used to compare cognitive functions (standard scores) between 3 stages of reproductive life, between the level of education and between 3 genotypes of XbaI ERα polymorphism, between 3 genotypes of PvuII ERα polymorphism. The t test was applied to compare cognitive functions

between two genotypes of APOE polymorphism. The χ^2 test was used to compare the genotypes of APOE, XbaI and PvuII ERα polymorphisms between 3 stages of reproductive life of the women studied, as well as Pearson correlation coefficient r was applied to check if there is a correlation between cognitive functions and age of the women studied.

The value of $p<0.05$ was considered as a significant difference.

Informed consent for participation in the study was obtained from all women. The study was approved by the Ethics Committee of the Institute of Rural Medicine in Lublin, Poland.

Results

The Neurocognitive Index in the studied women was between 28 an 114 points, mean 92.62±13.05 points, which is an average result. Most of the women (63.67%) received an average NCI grade, 18% - low average, 10.33% - low, 4.33% - very low and 3.67% above average. The studied women obtained the best results in simple attention (mean 100.76±11.82 points) and the lowest in terms of reaction time (mean 88.73±17.04 points). Between these results there were results concerning the remaining 9 cognitive functions (means from 92 to 96 points), (table 1). Most women (92.33%) reported simple attention on an average level. Some 7.66% had simple attention: low average (2.33%), low (3.33%) or very low (2.00%). Almost a half of the participants (47%) had a reaction time on an average level. Among the group, 7.67% had above average reaction time. 45.34% of the participants had reaction time: low average (19.67%), low (14%) or very low (11.67%).

Both the numbers (in points), as well as the distribution of grading for cognitive functions, did not differ significantly between women at three different stages of reproductive life.

The neurocognitive index and 9 out of 11 cognitive functions (except for visual memory and simple attention) were correlated to educational level of the women studied ($p < 0.05$). The participants with higher education reported significantly better NCI results and 9 cognitive functions than those with lower education.

The Neurocognitive Index and 8 cognitive functions were negatively correlated to age in the women studied ($r < 0$, $p < 0.05$). This pertains to 3 types of memory: complex, verbal and visual, as well as 3 speeds: psychomotor, motor, processing, reaction time and cognitive flexibility. This means, the older the women were, the lower their neurocognitive index and the above mentioned cognitive functions were. However, there was not found a correlation between age and 3 cognitive functions: executive function, as well as simple and complex attentions.

Polymorphism of the following genes was looked at in candidates of cognitive dysfunctions: apolipoprotein E and estrogen receptor α (in two genotypes: XbaI i PvuII).

In the group of women doing white-collar jobs, two APOE polymorphisms were noticed: $\varepsilon_2/\varepsilon_3$ (in 10.33% of women) and $\varepsilon_3/\varepsilon_3$ (in 89.67%). Neither $\varepsilon_3/\varepsilon_4$ nor $\varepsilon_4/\varepsilon_4$ were found (table 2).

Regarding the genotype PvuII of estrogen α receptor polymorphism (table 3), it was reported TC type in almost a half of the participants (49%), AG in 42% and CC was rarely reported (in 22%). Analyzing the types of genotype XbaI of estrogen α receptor polymorphism (table 4), it was mostly the AA type (in 45% of the women), less often AG type (in 29%) and the GG type rarely (in 13%). The presence of APOE polymorphism as well as ERα PvuII and XbaI polymorphisms did not differ significantly between three different stages of reproductive life in the women studied.

Analyzing the relation between the cognitive functions and presence of genotypes $\varepsilon_2/\varepsilon_3$ and $\varepsilon_3/\varepsilon_3$ APOE polymorphism (table 5), ERα XbaI (table 6) and PvuII polymorphism (table 7), only the correlations between reaction time and presence of both types of estrogen α receptor polymorphism were found (Figure 1). Best grades for reaction time were reported in women with AA genotypes (90.9 points on average) and TT (92 points on average). Lower grades were given for women with AG genotypes (87.88 points on average) and TC (88.44 points on average), while the lowest grades for this cognitive function were

Table 1.
Standard scores' results for cognitive functions in the study participants

Cognitive functions	Para-meter	Early peri-menopau-sal period	Late perime-nopausal period	Postmeno-pausal period	Total	Group com-parison
NCI	min	40.00	75.00	28.00	28.00	F=1.968 p=0.142
	max	113.00	114.00	114.00	114.00	
	M	93.56	95.28	91.30	92.62	
	SD	12.96	9.29	13.87	13.05	
Complex memory	min	57.00	59.00	52.00	52.00	F=0.920 p=0.400
	max	133.00	135.00	128.00	135.00	
	M	97.50	94.53	95.13	95.83	
	SD	14.30	16.50	15.50	15.25	
Verbal memory	min	61.00	55.00	49.00	49.00	F=1.562 p=0.211
	max	122.00	125.00	127.00	127.00	
	M	98.97	95.47	95.86	96.84	
	SD	12.45	17.10	15.52	14.84	
Visual memory	min	46.00	62.00	58.00	46.00	F=0.119 p=0.888
	max	131.00	131.00	131.00	131.00	
	M	97,25	96.00	96.63	96.75	
	SD	15.16	15.64	14.15	14.67	
Psychomotor speed	min	40.00	32.00	51.00	32.00	F=1.827 p=0.163
	max	127.00	123.00	132.00	132.00	
	M	95.01	92.56	91.45	92.80	
	SD	14.73	15.13	14.31	14.61	
Reaction time	min	42.00	67.00	20.00	20.00	F=2.938 p=0.054
	max	119.00	119.00	117.00	119.00	
	M	89.78	93.47	86.76	88.73	
	SD	16.92	11.38	18.15	17.04	
Complex attention	min	22.00	27.00	19.00	19.00	F=0.049 p=0.388
	max	120.00	121.00	118.00	121.00	
	M	93.54	98.23	93.18	94.02	
	SD	21.28	18.96	22.70	21.73	
Cognitive flexibility	min	36.00	32.00	24.00	24.00	F=0.993 p=0.372
	max	124.00	126.00	122.00	126.00	
	M	92.64	95.98	91.02	92.27	
	SD	20.48	18.68	21.33	20.69	
Processing speed	min	57.00	64.00	45.00	45.00	F=0.952 p=0.387
	max	132.00	125.00	128.00	132.00	
	M	92.44	93.42	90.52	91.57	
	SD	12.71	13.72	15.62	14.44	
Executive function	min	36.00	30.00	26.00	26.00	F=0.823 p=0.440
	max	124.00	125.00	121.00	125.00	
	M	93.04	96.40	91.90	92.92	
	SD	20.41	18.52	20.88	20.39	
Simple attention	min	19.00	77.00	24.00	19.00	F=0.496 p=0.610
	max	107.00	107.00	108.00	108.00	
	M	101.68	100,74	100.17	100.76	
	SD	11.05	9.15	12.91	11.82	
Motor speed	min	46.00	68.00	40.00	40.00	F=1.968 p=0.142
	max	136.00	123.00	128.00	136.00	
	M	98.10	96.33	94.39	95.91	
	SD	15.19	12.98	14.77	14.72	

Table 2.
The genotype apoE in the study participants

APOE	Early perimenopausal period		Late perimenopausal period		Postmenopausal period		Total	
	n	%	n	%	N	%	n	%
ε2/ε3	8	8.00	5	11.63	18	11.46	31	10.33
ε3/ε3	92	92.00	38	88.37	139	88.54	269	89.67
Total	100	100.00	43	100.00	157	100.00	300	100.00

$\chi^2 = 0.883$, $p = 0.643$

Table 3.
The genotype PvuII of estrogen α receptor polymorphism in the study participants

PvuII	Early perimenopausal period		Late perimenopausal period		Postmenopausal period		Total	
	n	%	n	%	N	%	n	%
TT	29	29.00	16	37.21	42	26.75	87	29.00
TC	53	53.00	14	32.56	80	50.96	147	49.00
CC	18	18.00	13	30.23	35	22.29	66	22.00
Total	100	100.00	43	100.00	157	100.00	300	100.00

$\chi^2 = 6.152$, $p = 0.188$

Table 4.
The genotype XbaI of estrogen α receptor polymorphism in the study participants

XbaI	Early perimenopausal period		Late perimenopausal period		Postmenopausal period		Total	
	n	%	n	%	N	%	n	%
AA	45	45.00	23	53.49	66	42.04	134	44.67
AG	42	42.00	12	27.91	73	46.50	127	42.33
GG	13	13.00	8	18.60	18	11.46	39	13.00
Total	100	100.00	43	100.00	157	100.00	300	100.00

$\chi^2 = 5.978$, $p = 0.279$

Table 5.
Cognitive functions according to polymorphism of the Apolipopteine E gene in the study participants

Cognitive functions	APOE				Significance of the differences	
	ε2/ε3		ε3/ε3			
	M	SD	M	SD	t	p
NCI	94.39	8.37	92.42	13.48	0.794	0.428
Complex memory	92.39	13.57	96.23	15.41	1.330	0.185
Verbal memory	94.81	14.62	97.07	14.88	0.805	0.421
Visual memory	93.65	11.89	97.10	14.93	1.244	0.214
Psychomotor speed	92.26	16.37	92.86	14.43	0.216	0.829
Reaction time	91.00	15.31	88.46	17.24	0.784	0.434
Complex attention	98.19	14.77	93.54	22.37	1.129	0.260
Cognitive flexibility	97.26	16.39	91.70	21.08	1.420	0.157
Processing speed	90.74	11.30	91.67	14.77	0.338	0.736
Executive function	98.45	15.98	92.29	20.77	1.598	0.111
Simple attention	99.97	11.10	100.85	11.91	0.392	0.695
Motor speed	98.10	13.97	95.65	14.81	0.874	0.383

Table 6.
Cognitive functions according to ERα XbaI polymorphism in the study participants

Cognitive functions	XbaI						Significance of the differences	
	AA		AG		GG			
	M	SD	M	SD	M	SD	F	p
NCI	93.52	11.40	92.68	14.70	89.36	12.44	1.544	0.215
Complex memory	95.61	14.83	97.00	16.05	92.79	13.90	1.160	0.315
Verbal memory	96.29	14.45	97.84	15.35	95.46	14.66	0.548	0.579
Visual memory	96.86	14.67	97.63	14.43	93.49	15.34	1.199	0.303
Psychomotor speed	92.14	15.42	93.60	14.61	92.44	11.67	0.336	0.715
Reaction time	90.90	15.70	87.88	18.69	84.03	14.88	2.757	0.049
Complex attention	95.72	19.08	93.32	23.50	90.46	24.20	1.000	0.369
Cognitive flexibility	93.09	18.62	92.91	22.00	87.38	22.84	1.254	0.287
Processing speed	90.66	15.42	92.24	14.10	92.54	12.02	0.492	0.612
Executive function	93.57	18.31	93.72	21.67	88.08	22.63	1.270	0.282
Simple attention	100.82	11.44	100.71	11.40	100.69	14.50	0.004	0.996
Motor speed	96.05	15.34	96.09	14.87	94.82	12.14	0.121	0.886

Table 7.
Cognitive functions according to ERα PvuII polymorphism in the study participants

Cognitive functions	PvuII						Significance of the differences	
	TT		TC		CC			
	M	SD	M	SD	M	SD	F	p
NCI	94.89	9.44	92.06	14.54	90.89	13.43	2.036	0.132
Complex memory	96.41	14.34	95.14	15.75	96.62	15.47	0.303	0.739
Verbal memory	96.29	14.62	97.04	15.04	97.12	14.90	0.085	0.918
Visual memory	98.03	14.65	95.54	14.41	97.74	15.25	0.987	0.374
Psychomotor speed	94.13	13.49	92.28	16.17	92.20	12.29	0.506	0.603
Reaction time	91.86	14.65	88.44	17.51	85.24	18.37	2.910	0.048
Complex attention	97.78	17.48	92.89	22.47	91.59	24.63	1.925	0.148
Cognitive flexibility	94.66	17.47	92.28	21.12	89.11	23.36	1.353	0.260
Processing speed	91.24	15.80	91.20	14.82	92.85	11.54	0.329	0.720
Executive function	94.89	17.23	93.16	20.67	89.80	23.33	1.187	0.306
Simple attention	101.26	11.79	100.11	11.57	101.53	12.50	0.441	0.644
Motor speed	97.40	14.73	95.58	15.48	94.67	12.90	0.718	0.488

received by women with GG genotypes (84 points on average) and CC (85 points on average).

Discussion

The increase in prevalence of cognitive dysfunctions along with age has been confirmed by numerous researchers. It was also noticed that women are more likely to suffer from lowering of cognitive functions and dementia-related syndromes [37]. Numerous authors have pointed to the fact that women in perimenopausal and postmenopausal age fare way worse than younger ones, when it comes to memories, attention or reaction speed [38,39,40].

Due to the unanimous role of the endogenic estradiol concentration in the blood in development of cognitive functions it is often suggested that this situation is due to different expression of ER α and β in the women [41]. Some researchers claim that lowering the estrogen production levels that often accompanies menopause, increases the ER expression in the brain, which leads to an increase in estrogen concentration in the brain [42]. The Erα expression

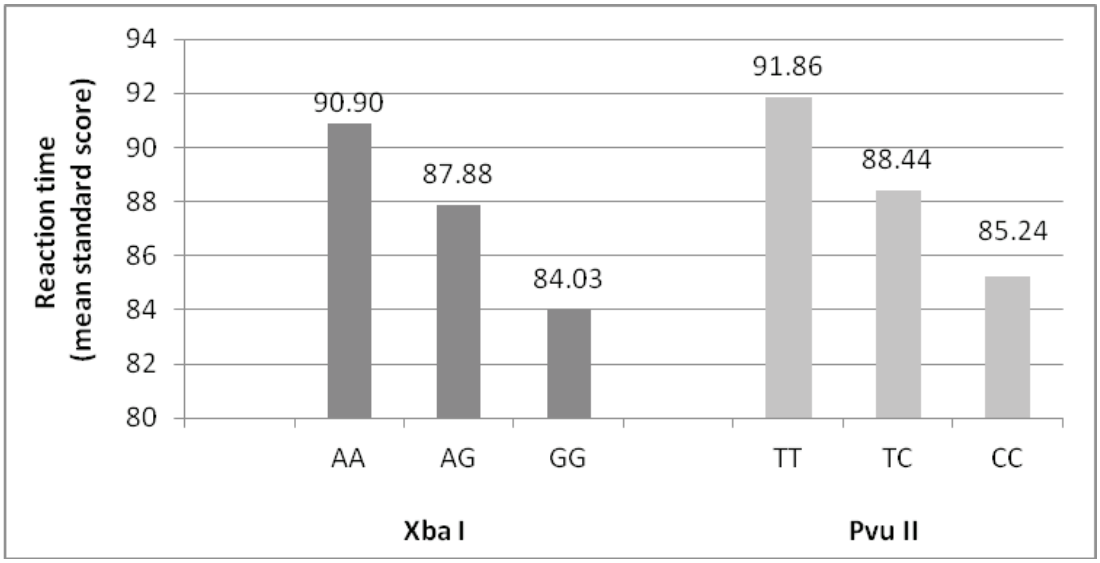

Fig. 1.
Average reaction time according to ERα PvuII and XbaI polymorphisms in the study participants

in hippocampus decreases in some of the conditions that affect human memory, including the AD [42], while the expression of ERβ may increase in AD [43]. The ERα polymorphisms can affect the degree of deterioration the functioning of receptors [32-34, 44].

Regarding the presence of Xbal and PvuII ERα polymorphisms in the studied women, most had genotype AA (45%), AG (42%), while the least had GG (13%) XbaI. In case of PvuII, most had TC genotype (50%), less often AG (in 42%) and least had CC (some 22%).

Analyzing the prevalence of XbaI and PvuII polymorphisms in the population shows some differences, depending on types of scientific works. For instance, Myśliwska claims that regarding the PvuII polymorphism some 20% of white women have CC homozygotes, over 20% have TT homozygotes, while the remainder have TC homozygotes [36]. Similarly, Koch and Shearman suggest that the TC genotype is the most popular one, then TT and the least frequent is the CC type [45, 46]. According to Schuit, least people have TT genotype, while most have TC genotype [47]. Lamon-Fava shows that regarding the PvuII polymorphism most people have TC genotype, while least have CC genotype. The same author suggests that regarding the XbaI polymorphism most women had the AG genotype and least had GG genotype [48].

Analyzing the relationship between the XbaI and ERα PvuII polymorphisms cognitive functions, we found a correlation between reaction time and presence of both types of estrogen α receptor polymorphism. The best reaction time appeared in women with AA genotypes (XbaI) and TT (PvuII). Lower results in reaction time appeared in women with AG (XbaI) and TC (PvuII) genotypes, while the lowest results were obtained by women with GG genotypes (XbaI) and CC (PvuII). However we did not found correlations between other cognitive functions and the estrogen receptor α gene polymorphism.

In the other study, Bojar et al. obtained the results suggesting influence of the estrogen receptor α gene polymorphism over other cognitive functions: general memory, verbal memory and processing speed. Women with GG genotype (XbaI) obtained lower results in these cognitive functions than those with AA (XbaI) and AG (XbaI) genotypes [49]. However those authors did not found a correlation between cognitive functions and PvuII ERα polymorphism.

A study by Bousman shows that women with the T PvuII allel had significantly worse logical memory, when compared to allel C women [50]. Ryan, similarly to the authors of this work in their analysis, noticed no relationship between Xbal, PvuII Erα polymorphism and lowering the results of selected cognitive functions: visual memory, psychomotor speed, executive functions, global functions, verbal fluency [51]. Monastero also noticed no relationship between PvuII polymorphism and AD [52]. A similar lack of relationship between Xbal and PvuII polymorphisms

and the risk of AD development has been mentioned by other authors [53-55]. Also, some authors claim that no polymorphism led to any other dementia conditions, other than the Alzheimer's disease. This means, it caused none of the following dementia: alcohol-related dementia, Parkinson's disease-related dementia or vascular dementia [56,57,33]. Other authors claim that the presence of Pvull and XbaI polymorphisms significantly boosts the risk of AD. [58]. Basing on a large metaanalysis, Sundermann noticed a significant relationship between Xbal and PvuII Erα polymorphisms and the risk of dementia development, particularly of the AD type. Also, Yaffe points to the influence of Xbal or PvuII polymorphism over the development of AD and worse results of cognitive functions, as analyzed using the Modified Mini-Mental Status Examination [59]. The relationship between the Xbal and PvuII polymorphisms and the risk of dementia development in Asian population was also noticed by Luckhaus [57].

In this study, we also looked for a correlation between the APOE gene polymorphism and cognitive functions impairment. Among the group of white-collar workers two APOE polymorphisms were reported: $\varepsilon_2/\varepsilon_3$ (in 10 % of women) and $\varepsilon_3/\varepsilon_3$ (in 90 %). The following APOE polymorphisms were not found in the group: $\varepsilon_3/\varepsilon_4$ i $\varepsilon_4/\varepsilon_4$. In the general population, the prevalence of certain alleles is determined as e3 – 75%, e4 – 15%, e2 – 8% [60]. The homozygotic genotype dominates $\varepsilon_3/\varepsilon_3$ (60 %), heterozygotes $\varepsilon_3/\varepsilon_4$ and $\varepsilon_3/\varepsilon_2$ are 20 and 13 % respectively. Homozygotic genotype $\varepsilon_4/\varepsilon_4$ is rare: 2–3% , $\varepsilon_2/\varepsilon_2$ – 1%, as well as heterozygotic $\varepsilon_2/\varepsilon_4$ 1–2 % [61].

In this study, we did not find any correlation between the APOE genes in women and cognitive function impairment. It needs emphasizing that in the study group only two polymorphisms were reported and no woman had the ε_4 allel, which is often blamed for cognitive impairments, like the AD. According to Nalbantolghu, the prevalence of the ε_4 allel in patients with AD hovers around 33% and 40%, as compared against 5-14% in control groups. The risk of developing the Alzheimer's diseases in case of one allel ε_4 increases 2-3 times, while in case of heterozygotes $\varepsilon_{4/}$ ε_4 5-10 times, as compared with the rest of the population. Furthermore, in cases of heterozygotes the first symptoms of cognitive impairments appear much earlier and the average age of AD development is around 68 years [62]. Porier has also noticed that in case of AD patients, the allel ε_4 happened in 75% of women and 45% of men [63]. The increased frequency of allel ε_4 was also noticed in women suffering from other neurodegenerative disorders and mild cognitive dysfunctions [64-66]. It is also postulated that the ε_2 allel has a protective role in relationship to cognitive dysfunctions [67]. The presence of ε2/ε3 genotype positively influenced the results of cognitive function examination (CNS-VS), while genotypes ε3/ε4 and ε4/ε4 correlated with lower results in the test [68].

The progress in molecular biology inspires researchers to look for new risk factors in cognitive dysfunctions. Due to the huge discrepancies between authors regarding the influence of estradiol concentration and its expression in the central nervous system, as well as the ER α XbaI and PvuII genes and APOE gene polymorphism over cognitive functions, there is a need for further research in the subject. Only a common attitude would allow for suggesting successful prophylactic actions and looking for new methods of curing cognitive dysfunctions in the population. Due to the ageing of the general population, this is one of the biggest challenges that contemporary medicine faces.

Conclusion

1. Cognitive functions in the participants received average grades. The female participants scored the best in terms of simple attention and the lowest in terms of reaction time.
2. Some cognitive functions were negatively correlated with age.
3. The higher one's education, the better results of cognitive functions.
4. PvuII and XbaI ERα polymorphism affected the results in terms of reaction time.

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