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Correlation of Depression, Behavioral Disorders and Delirium with Certain Genetic Abnormalities in Patients with Alzheimer's Disease

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Abstract

Objectives: The aim of this study was to find out how some of the genetic polymorphisms influence the clinical picture of the dementia syndrome, in other words how some clinical features correlate with certain genetic abnormalities.

Methods: Altogether 183 people were examined; they were either ambulatory patients of the Psychiatric clinic or people of corresponding age. Patients that suffered with Alzheimer's disease numbered 86, healthy control subjects numbered 97. A single blood sample was collected from each of the test subjects in order to be used for genetic testing.

Results: The statistical analysis of the data about the influence of individual polymorphisms on the development of depression, behavioral disorders and delirium at the group of patients with Alzheimer's disease was made. The acquired results provide the possibility to assume that the presence of the G/G polymorphism in neurotropic factor of the brain and the A/G in 5-HT2A-receptors can manifest as a protective factor of delirium incidence among the patients with AD. The carriers of the aforementioned polymorphisms of the examined group of patients the deliriums weren't present among 70.21% and in 69.05% of the cases.

Conclusion: Our study was of a pilot character. The most important of our result was the finding of higher number of polymorphisms G/G for BDNF and A/G for 5-HT2A serotoninergic receptors among patients, that didn't suffer from deliriums. A follow up research will focus on this findings. The study was supported by a grant Progress Q27.

Keywords: Alzheimer's disease; Clinical studies; Gene mutations; Polymorphisms; Genetic factors of the Alzheimer's disease; Clinical features of the Alzheimer's disease; Association studies

Introduction

Alzheimer's Disease (AD)–the most common form of dementia is a neurodegenerative disease that manifests itself by damaging neurons in certain parts of the brain. The worse damage is observed in the area of both hippocampi and adjacent areas of medial structures of temporal lobes. This illness was first described by the German psychiatrist Alois Alzheimer. There are two forms of this disease–an early form and a late form. The late form of this disease occurs among patients older than 65 years, the early form (the percentile form) occurs among patients younger than 65 years. The early form, which is rare (just a few percent) consists of cases that are predominantly genetically determined. The form with the late offset is seldom genetically determined instead.

Alzheimer's disease is one of the proteinopathies and as such there are pathological changes of some of the proteins followed by accumulation of these proteins in the brain. Degeneration of Amyloid Beta (AB) and intraneuronal Tau protein occurs during Alzheimer's disease. This sets in motion the entire neurodegenerative cascade–the production of inflammatory cytokines followed by the development of inflammation, mitochondrial damage and malfunction of energy generation and excessive release of free oxygen and nitrogen radicals followed by oxidation stress, decreased production and release of nerve growth factor, changes in neurotransmissions (malfunction of the central acetylcholinergic and glutamatergic system) and many other neurodegenerative features. As a result there is a decreased neurogenesis and lower neuronal plasticity, which represent the main features of dementia syndrome. Numeric atrophy of neurons develops as well as macroscopic atrophy especially of hippocampi and other medial temporal structures and parietal cortex.

The protein degeneration actually precedes the clinical manifestations of dementia. Clinically speaking, the Alzheimer's disease exists in a latent–pre-clinical stage (amyloid beta deposits are detectable using PET method), later progresses to prodromal stage–amnesic form with low grade malfunction of cognitive functions and gradually progresses to a clinical picture of dementia.

Main risk factors of Alzheimer's disease are, apart from age, genetic predispositions. Nowadays a range of genes is known that are connected to the development of the disease. They are either mutations or genetic predispositions in a form of polymorphisms.

Clinically, the Alzheimer's disease manifests itself as a progressive dementia that mostly starts by recent episodic memory and operational memory loss. Gradually other cognitive function disorders, such as other types of memory loss, attention, speech, ideomotorics etc. occur. Apart from that, two other groups of symptoms develop. These are: Daily life activities disorders and so called Behavioral and Psychological Symptoms of Dementia (BPSD). Symptoms such as unrest, agitation, aggression, other associated psychotic symptoms (hallucinations,

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delusions, misinterpretations) and emotivity disorders (depression, anxiety, dysphoria, sleeping disorders or sleeping/vigilance cycle disorders). Deliria occur frequently.

In this scientific work we focused on the occurrence of depression, behavioral disorders and also the associated deliria. Depression is documented quite often in association with the Alzheimer's disease (in 20%-40% of cases) [1]. In the early stages (mild amnesic disorder of the cognitive functions, mild dementia) the realization of the cognitive functions deficiency, most importantly of memory loss, can have its influence. In the late stages deficiency of several neuro mediators (especially serotonin and noradrenalin deficiency), inflammatory reaction and other mechanisms of neuro degeneration influence the development of depression.

Among the patients with the Alzheimer's disease behavioral deficiencies are common, especially in cases of medium and high severity. Agitation-constant unrest that can even be quite mild but nonetheless disruptive is a very frequent symptom. Sometimes agitation manifests itself as a considerable unrest with screams, swearing, emitting inarticulate sound, running from home, and escaping hospitals or social care centers. Aggression, most often just verbal aggression, but also destruction of objects and the least often aggressively against people sometimes occurs. In other cases the patients make some aimless stereotypical actions, such as moving objects from one place to another. As a part of behavioral disorders psychotic symptoms can also occur (some sources claim in frequency of 30%). This behavior usually consists of significantly unsystematic paranoid-persecutory delusions (somebody steals things from patients etc.). Among the hallucinations, the ones most frequent are visual, very rarely the multisensory complex hallucinations with the feeling of situation involvement occur.

Deliria that are associated with the dementia don't occur very often among patients suffering with clean Alzheimer's disease. Their occurrence however increases in cases of vascular component presence, inappropriate medication and somatic comorbidity [2].

Overview of Observed Polymorphisms

The first gene that was found which has its influence on the development of the AD is a gene of the trans-membrane protein, Amyloid Precursor Protein (APP). Amyloid precursor protein is the best known thanks to the fact, that its fragment, beta-amyloid is a basic constituent of the amyloid plaques during Alzheimer's disease. The amyloid precursor protein gene that was localized on the short arm of the chromosome 2121q21.1 includes at least 19 exons and can vary into up to 10 isoforms of APP with a different length of the molecule. These isoforms make up a complex group of first class membrane glycoproteins. The four isoforms of APP that include 695, 714, 751 and 770 amino acid residues contain the sequence of the beta-amyloid. APP was expressed in almost all of the animal cells that were researched until now. Amyloid precursor protein has a trans-membrane location in neurons. In its extraneuronal part it is broken down by alpha secretes enzymes into soluble fragments measuring 1-39 amino acids. These fragments have their physiological roles. Some other enzymes that follow by breakdown of APP. These are beta and gamma secretases. As a result of this breakdown there are some longer fragments measuring 40-42 amino acids. These fragments subsequently oligomerize and oligomers created this way are very toxic, especially for mitochondrias and synapses. Beta amyloid oligomers stop being soluble and synthesize into fibrils and these later coagulate in intercellular spaces of cortex and later they polymerize and create amyloid plaques.

APP mutation is the cause of AD development in 1%-3% of the cases. 12 pathogenic mutations of APP are known nowadays [3].

It was also found that a polymorphism of another gene APOE, which was found on chromosome 19 is associated with a late form of AD. Apolipoprotein E is an apolipo-protein of the blood serum and it is a part of chylomicrons and very low density lipoproteins. It is one of the most important apolipo-proteins that independently contribute to the lipid metabolism in blood, on the other hand it also contributes to a cholesterol metabolism in the brain. It has a distinctive anti-sclerotic effect. ApoE is very similar to cholesterol. It is a ligand to a number to different types of receptors, including LDL-receptors which gives the leading role in receptor connection of chylomicron residues with very low density lipoproteins in hepatocytes and peripheral tissues. ApoE is synthesized in brain by the astrocytes and microglia and its receptors are produced by neurons. There are three basic isoforms of this protein–apoE2, apoE3 and apoE4. ApoE4 isoform is an important genetic risk factor of AD development, which can be connected up to a half of the cases of the late sporadic form of AD [4]. ApoE4 isoform can be found in our population among 16%-17% of the people. Presence of one allele of ApoE4 increases the risk of AD three times, homozygote individuals have up to fifteen times higher chance of AD development. The most common isoform ApoE3 seems indifferent in the connection to AD, ApoE2 isoform probably has a mild protective effect. Presence of ApoE4 allele isn't a condition that will necessarily result in AD, but it greatly increases the risk of development of this disease.

In the last couple of years there has been an intensive research in the connections that might be able to prevent or at least slow down creations of amyloid plaques. The scientists are greatly interested in Heat Shock Proteins (HSP) because thanks to their chaperone characteristics HSP prevent creation of Abeta formations *in vitro* and these proteins support AB phagocytosis through the activation of microglia [5].

Heat shock proteins are a class of functionally similar proteins. Their expression intensifies during a temperature rise or under other conditions that might stress the cell.

Increased expression of heat shock protein genes is regulated at the transcription stage. Exceptional increase of the expression is a part of a cellular response to a heat shock and is usually a factor of the heat shock [6]. These proteins were found in the cells of all living organisms ranging from bacteria to a man.

Heat shock proteins work as intracellular chaperons in a relationship towards the other proteins. They play an important role in protein-protein interactions, for example during folding and building of different proteins, they prevent the unwanted aggregations of proteins. HSP stabilize partially coagulated proteins and facilitate their transport through intracellular membranes [7,8].

The ability of HSP70 to create a permanent complex with tau-protein protects the tau-protein against the hyperphosporylation and lower content of HSP70 leads to creation of neurofibrillar tangles in neurons. They also help the transport of damaged proteins to the areas of their utilization. In the central nervous system these protein also carry out the neuroprotective task. HSP can also restrict NO synthesis and reduce inflammation reactions during AD in an appropriate way. It was also found that cells with higher HSP70 content are more resistant against glutamate excite toxicity, which is one of the factors of damage to the neurons during AD. HSP and especially HSP70 most likely represent an important endogenic protective system for neurons during AD, because its increase was proved in brains of patients suffering with AD [9].

Brain-derived neurotrophic factor is a human protein that is coded by BDNF gene. BDNF is one of the neutrophines, which are substances that stimulate and support the formation of neurons. BDNF influences certain neurons of central and peripheral nervous system, it also helps newly developed neurons to survive and increases the number and differentiation of new neurons and synapses. BDNF is important for the long term memory [10]. According to the research BDNF plays a major role in a pathomorphology of mood disorders connected to stress. During the acute stress situation there was a rapid increase of levels of BDNF in serum and at the same time long periods of stress lead to the development of depression and gradual drop in BDNF levels [11].

Change in volume of BDNF in brain is able to cause the development of the pathological process of Alzheimer's Disease (AD) or contribute to it in a significant way [12]. Gene that codes the BDNF synthesis is one of the key factors supporting long-term plasticity in hippocampus. It is exactly this structure that is key in development of early symptoms of AD. During the experiment BDNF had a protective effect on cholinergic system of the brain during the formation of AD [13]. The post mortem examination of the brains of patients suffering with AD had shown that BDNF content was lower in hippocampus, temporal and frontal cortex [14,15]. One of the reasons of the lower content of BDNF when suffering with AD is a suppression of production of this neurotrophin by dendritic cells under the influence of beta-amyloid which leads to trophic influence deficiency [12]. Decrease of mRNA level during AD was found in hippocampus, parietal cortex and basal ganglia [16]. There is a a possibility of decreasing the BDNF content thanks to its deposition. With the aid of immunochemical reactions in senile plaques in the cortex connections similar to BDNF [17] were found. Thanks to the decreasing of mRNA level that codes the TrkB receptors it is possible to consider a participation of this mechanism in the degenerative processes in the brain. However, it is difficult to say, which process is the primary one–the decreasing production of BDNF and subsequent decrease of receptor synthesis or vice versa, primary decrease of receptor synthesis leads to another malfunction of BDNF synthesis [13].

Scientists described BDN–val/met polymorphism that is located in codon 66 and people carrying this gene have higher risk of AD development (approx. 35% of the population). Presence of this polymorphism is especially dangerous in combination of ApoE4 allele [18].

5-HT2A-receptor among mammals is one of the subtypes of 5-HT2-receptors, subgroup of serotonin receptors. It is metabotropic with G-protein associated receptor [19]. Receptor of this subtype (5HT2A) is a basic stimulating subtype of all G-protein associated serotonin receptors (5-HT). On the other hand 5-HT2A subtype receptors are able to have inhibiting, decelerating effect [20] in some parts of the brain, such as the visual cortex or orbitofrontal cortex. More than 250 polymorphisms of 5-HT2A gene. 5-HT2A gene mutations are associated with higher susceptibility to depressions [21].

According to the research is a 5-HT2A-receptor among AD patients associated with a number of neuropsychologic symptoms, such as depression, aggression/agitation or psychosis [22,23].

An important part of the pathogenesis of neurodegenerative changes during Alzheimer's disease is a neurotransmitter function deficiency. Specifically an important part in cognitive and behavioral disorders are played by serotoninergic system deficiencies. Earlier it was found that VNTR-polymorphism of serotonin transporter gene (5HTT), which plays an important role in a serotoninergic neurotransmission, is associated with depressions [24]. It is known, that VNTR can have its influence on gene expression. VNTR-polymorphism is connected with affective disorders [25] and schizophrenia [23].

VNTR (Variable Number Tandem Repeat) are genomes on different chromosomes that have short nucleotide sequences organized in tandem repetitions. There are inter-individual variations in number of repeats. Every variation has a character of an innate allele. C allele of inflammatory cytosine IL6 in a variable number of tandem repeats (polymorphism) dependency can be connected with postponed development and lower risk of AD.

Low density lipoprotein receptor protein that mediates endocytosis of low density lipoproteins that are enriched with cholesterol. LDL-receptor is a membrane protein and is one of the important regulatory features of lipid metabolism in the blood. The association of LPR polymorphism with the Alzheimer's disease is confirmed. This polymorphism is considered to be a risk factor of AD development. A number of meta-analysis shows that LPR polymorphism isn't a basic risk factor of this disease, although its influence cannot be entirely ruled out [26].

The clinical studies that took place at our clinic were aimed to determine the way in which certain polymorphisms modify the clinical picture of dementia and how some clinical features correlate with certain genetic abnormalities. The material has been studied from previously taken samples in patients diagnosed with Alzheimer's disease and the control group of healthy individuals [27].

Methods

Altogether 183 people were examined; they were either ambulatory patients of the Psychiatric clinic or people of corresponding age. Out of these 65 were men and 118 were women of an average age of 68.7 years. Patients that suffered with Alzheimer's disease numbered 86, healthy control subjects numbered 97. Patients with the Alzheimer's disease suffered with light or intermediate stages of dementia. Patients suffering with sever dementia were not included in the study. A single blood sample was collected from each of the test subjects in order to be used for genetic testing. Sample was collected under a condition of signing an informed consent form. Patients were under a long-term psychological observation and had regularly taken cognitive tests (ACE-R, MMSE). Patients were also observed for non-cognitive symptoms, including behavioral disorders, depression and deliriums. All patients had undergone brain imaging tests-computer tomography or MRI in order to eliminate the possibility of other reasons for dementia. The genetic information that was examined was: Apolipoprotein Epsilon (ApoE), heat shock proteins HSP 70 190and HSP 70 110, brain neutrophilic factor BDNF, serotonin receptor 5HT2a, VNTR polymorphism of the serotonin transporter gene and the low density lipoprotein receptor.

Results

Tables 1-7 below is the statistically processed data about the occurrence of individual polymorphisms at two groups of subjects–the ones diagnosed with Alzheimer's disease and the control group of healthy individuals. 183 patients participated in the research, out of these number 65 men and 118 women; their average age was 68.7 years. A direct link between individual polymorphisms and the development of the Alzheimer's disease wasn't proved.

The statistical analysis of the data about the influence of individual polymorphisms on the development of depression, behavioral disorders and delirium at the group of patients with Alzheimer's disease was also made. A direct link between individual polymorphisms and the development of depressions, behavioral disorders or delirium among

HSP 70 190	G/G	C/G	C/C
AD	42.6 %	45.4%	12%
Control	35.4%	50.6%	14%

Table 1: Incidence of individual allelic combinations of HSP 70 190 in percentage of patients with alzheimer's disease and healthy control.

HSP 70 110	A/A	A/C	C/C
AD	40%	48%	12%
Control	33%	51.7%	15.3%

Table 2: Incidence of individual allelic combinations of HSP 70 110 in percentage of patients with alzheimer's disease and healthy control.

LPR	L/S	L/L	S/S
AD	55%	34%	11%
Control	33%	51.7%	15.3%

Table 3: Incidence of individual allelic combinations of LPR in percentage of patients with alzheimer's disease and healthy controls.

BDNF	G/G	G/A	A/A
AD	62.6%	32%	5.4%
Control	63.5%	34%	2.5%

Table 4: Incidence of individual allelic combinations of BDNF in percentage of patients with alzheimer's disease and healthy control.

5HT2A	A/G	G/G	A/A
AD	56%	26.5%	17.5%
Control	44.7%	38.8%	16.5%

Table 5: Incidence of individual allelic combinations of 5HT2A in percentage of patients with alzheimer's disease and healthy control.

ApoE	3/3	3/4	4/4	2/3	2/4	2/2
AD	34.6%	41.4%	13.4%	8%	2.6%	0%
Control	67%	20%	1.2%	8.3%	2.5%	1%

Table 6: Incidence of individual allelic combinations of ApoE in percentage of patients with alzheimer's disease and healthy control.

VNTR	10/10	10/12	12/12	9/12	9/10
AD	13.4%	42.6%	40%	1.4%	2.6%
Control	16.5%	52%	28%	3.5%	0%

Table 7: Incidence of individual allelic combinations of VNTR in percentage of patients with alzheimer's disease and healthy control.

patients diagnosed with the Alzheimer's disease wasn't proved. The acquired results however provide the possibility to assume that the presence of the G/G polymorphism in neurotropic factor of the brain and the A/G in 5-HT2A-receptors can manifest as a protective factor of delirium incidence among the patients with AD. The carriers of the aforementioned polymorphisms of the examined group of patients the deliriums weren't present among 70.21% and in 69.05% of the cases.

The statistically processed data are included in the Tables 8-14, where 0-absence of depressions, behavioral disorders and deliriums, 1-mild form, 2-severe form, N–number of individuals.

Discussion

Association studies, that primarily aim to uncover the genetic predispositions to multifactorial illnesses, in other words study the genes, that increase or decrease the risk of illness are important in genetics. The knowledge of the link between individual polymorphisms and clinical features and genetic examination of polymorphisms will lead to the improvement of diagnostics and therapy.

Our study included 183 patients. This number will be extended later because the present number of patients is too low to make a solid conclusion. Our study was of a pilot character. The most important result was the finding of higher number of polymorphisms G/G for BDNF and A/G for 5-HT2A serotoninergic receptors among patients, that didn't suffer from deliriums. A follow up research will focus on this find. The study was supported by a grant Progress Q27.

Also the discovery of another polymorphism that influences the development and the clinical picture of AD would mean a discovery

Depression	0 (N)	1 (N)	2 (N)
G/G	43.75% (14)	31.25% (10)	25% (18)
C/G	35.29% (12)	35.29% (12)	29.41% (10)
C/C	11.11% (1)	77.78% (7)	11.11% (1)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
G/G	50.00% (16)	28.12% (9)	21.88% (7)
C/G	38.24% (13)	38.24% (13)	23.53% (8)
C/C	55.56% (5)	33.33% (3)	11.11% (1)
Delirium	**0 (N)**	**1 (N)**	**2 (N)**
G/G	62.50% (20)	25% (8)	12.50% (4)
C/G	70.59% (24)	17.65% (6)	11.76% (4)
C/C	66.67% (0)	33.33% (0)	0% (0)

Table 8: Correlation between incidence of individual allelic HSP 70 190 combinations and the occurrence of depression, delirium and behavioral disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
A/A	46.67% (14)	30% (9)	23.33% (7)
A/C	33.33% (12)	36.11% (13)	30.56% (11)
C/C	11.11% (1)	77.78% (7)	11.11% (1)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
A/A	50% (15)	26.67% (8)	23.33% (7)
A/C	38.89% (14)	38.89% (14)	22.22% (8)
C/C	55.56% (5)	33.33% (3)	11.11% (1)
Delirium	0	1	2
A/A	63.33% (19)	23.33% (7)	13.33% (4)
A/C	69.44% (25)	19.44% (7)	11.11% (4)
C/C	66.67% (6)	33.33% (3)	0% (0)
Depression	0 (N)	1 (N)	2 (N)
A/A	46.67% (14)	30% (9)	23.33% (7)
A/C	33.33% (12)	36.11% (13)	30.56% (11)
C/C	11.11% (1)	77.78% (7)	11.11% (1)

Table 9: Correlation between incidence of individual allelic HSP 70 110 combinations and the occurrence of depression, delirium and behavioral disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
L/S	28.57% (8)	39.29% (11)	32.14% (9)
L/L	36.84% (14)	39.47% (15)	23.68% (9)
S/S	55.56% (5)	33.33% (3)	11.11% (1)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
L/S	53.57% (15)	25.00% (7)	21.43% (6)
L/L	42.11% (16)	36.84% (14)	21.05% (8)
S/S	33.33% (3)	44.44% (4)	22.22% (2)
Delirium	0 (N)	1 (N)	2 (N)
L/S	71.43% (20)	17.86% (5)	10.71% (3)
L/L	65.79% (25)	21.05% (8)	13.16% (5)
S/S	55.56% (5)	44.44% (4)	0% (0)

Table 10: Correlation between incidence of individual allelic LPR combinations and the occurrence of depression, delirium and behavioural disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
A/A	50% (2)	50% (2)	0% (0)
G/A	50% (12)	25% (6)	25% (6)
G/G	27.66% (13)	44.68% (21)	27.66% (13)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
A/A	50% (2)	50% (2)	0% (0)
G/A	29.17% (7)	41.67% (10)	29.17% (7)
G/G	53.19% (25)	27.66% (13)	19.15% (9)
Delirium	**0 (N)**	**1 (N)**	**2 (N)**
A/A	100% (4)	0% (0)	0% (0)
G/A	54.17% (13)	25.00% (6)	20.83% (5)
G/G	70.21% (33)	23.40% (11)	6.38% (3)

Table 11: Correlation between incidence of individual allelic BDNF combinations and the occurrence of depression, delirium and behavioral disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
A/A	30.77% (4)	46.15% (6)	23.08% (3)
A/G	35.71% (15)	38.10% (16)	26.19% (11)
G/G	40.00% (0)	35% (0)	25% (0)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
A/A	38.46% (5)	46.15% (6)	15.38% (2)
A/G	50% (21)	33.33% (14)	16.67% (7)
G/G	40% (8)	25% (5)	35% (7)
Delirium	**0 (N)**	**1 (N)**	**2 (N)**
A/A	76.92% (10)	7.69% (1)	15.38% (2)
A/G	69.05% (29)	26.19% (11)	4.76% (2)
G/G	55% (11)	25% (5)	20% (4)

Table 12: Correlation between incidence of individual allelic 5-HT2A combinations and the occurrence of depression, delirium and behavioural disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
02-Feb	0% (0)	0% (0)	0% (0)
02-Mar	33.33% (2)	33.33% (2)	33.33% (2)
02-Apr	50% (1)	50% (1)	0% (0)
03-Mar	19.23% (5)	50% ()	30.77% ()
03-Apr	45.16% ()	32.26% (13)	22,58% (8)
04-Apr	50% (5)	30% (3)	20% (2)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
02-Feb	0% (0)	0% (0)	0% (0)
02-Mar	66.67% (4)	16.67% (1)	16.67% (1)
02-Apr	100% (2)	0% (0)	0% (0)
03-Mar	53.85% (14)	26.92% (7)	19.23% (5)
03-Apr	32.26% (10)	41.94% (13)	25.81% (8)
04-Apr	40% (4)	40% (4)	20% (2)
Deliriium	**0 (N)**	**1 (N)**	**2 (N)**
02-Feb	0% (0)	0% (0)	0% (0)
02-Mar	50% (3)	50% (3)	0% (0)
02-Apr	100% (2)	0% (0)	0% (0)
03-Mar	65.38% (17)	19.23% (5)	15.38% (4)
03-Apr	67.74% (21)	22.58% (7)	9.68% (3)
04-Apr	70% (7)	20% (2)	10% (1)

Table 13: Correlation between incidence of individual allelic ApoE combinations and the occurrence of depression, delirium and behavioural disorders in a group of patients with alzheimer's disease.

Depression	0 (N)	1 (N)	2 (N)
10-Oct	40% (4)	50% (5)	10% (1)
10-Dec	43.75% (14)	37.50% (12)	18.75% (6)
12-Dec	30% (9)	36.67% (11)	33.33% (10)
09-Oct	0% (0)	0% (0)	100% (2)
09-Dec	0% (0)	100% (1)	0% (0)
Behavioral disorders	**0 (N)**	**1 (N)**	**2 (N)**
10-Oct	30% (3)	60% (6)	10% (1)
10-Dec	40.62% (13)	21.88% (7)	37.50% (12)
12-Dec	53.33% (16)	36.67% (11)	10% (3)
09-Oct	100% (2)	0% (0)	0% (0)
09-Dec	0% (0)	100% (1)	0% (0)
Delirium	**0 (N)**	**1 (N)**	**2 (N)**
10-Oct	90% (9)	0% (0)	10% (1)
10-Dec	56.25% (18)	28.12% (9)	15.62% (5)
12-Dec	70% (21)	23.33% (7)	6.67% (2)
09-Oct	50% (1)	50% (1)	0% (0)
09-Dec	100% (1)	0% (0)	0% (0)

Table 14: Correlation between incidence of individual allelic VNTR combinations and the occurrence of depression, delirium and behavioural disorders in a group of patients with alzheimer's disease.

of a new biomarker of AD that would help in an early diagnostics and the early beginning of the therapy in a pre-clinical stage before the manifestation of dementia.

Out of the influenced clinical features we were interested in the occurrence of depressions, behavioral disorders and associated deliriums. Out of the genetic information polymorphism of the Apolipoprotein Epsilon (ApoE), heat shock proteins HSP 70 190 and HSP 70 110, brain neutrophilic factor BDNF, serotonin receptor 5HT2a, VNTR polymorphism of the gene of serotonin transporter and the low density lipoprotein receptor (OLD) were observed.

Patients were under a long-term psychological observation and had regularly taken cognitive tests (ACE-R, MMSE). The genetic information that was examined was: apolipoprotein epsilon (ApoE), heat shock proteins HSP 70 190 and HSP 70-110, brain neutrophic factor BDNF, serotonin receptor 5HT2a, VNTR polymorphism of the serotonin transporter gene and the low density lipoprotein receptor.

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