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BDNF rs 6265 polymorphism and COMT rs 4680 polymorphism in deficit schizophrenia in Polish sample

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Abstract:
Background: Deficit schizophrenia (DS) is distinguished from the group of schizophrenic psychoses based on the presence of primary negative symptoms. It differs from nondeficit (NDS) forms of schizophrenia in dimensions such as risk factors, family history, course of illness and neurobiological differences. The aim of the study was assessment of a potential association of the investigated polymorphisms of the brain-derived neurotrophic factor (BDNF) and catechol-O-methyltransferase (COMT) genes with the deficit syndrome in schizophrenia.
Methods: A cohort of 200 patients with schizophrenia (81 DS and 119 NDS subjects) and a group of 100 control subjects matched for ethnicity, sex and age were recruited. Somatic and psychometric assessment were conducted as well as structured interview about the influence of adverse biological, family and social factors. Genetic analysis of the BDNF (Val66Met) rs6265 and the COMT (Val158Met) rs4680 polymorphisms was performed.
Results: We found significant differences between DS and NDS in rs4680 COMT genotype distribution: more homozygous Val/Val were found (31 *vs.* 17%) in the NDS compared to the DS subgroup. No associations were found between the investigated polymorphisms of the BDNF gene and the presence of schizophrenia either in DS and NDS subgroups.
Conclusion: The analysis of the COMT rs4680 polymorphism in the present DS and NDS study shows that some genetic factors may be relevant in analyzing the reasons for the differentiation of schizophrenic subtypes.

Key words:
deficit schizophrenia, nondeficit schizophrenia, gene polymorphism, BDNF, COMT

Abbreviations: A – adenine, ALT – alanine transaminase, AST – aspartate transaminase, BDNF – brain-derived neurotrophic factor, COMT – catechol-O-methyltransferase, DS – deficit schizophrenia, G – guanine, ICD10 – International Statistical Classification of Diseases and Related Health Problems, Tenth Edition, Met – methionine, MINI – Mini International Neuropsychiatric Interview, MMSE – Mini-Mental State Examination, NDS – non deficit schizophrenia, OPCRIT – Operational Criteria for Psychotic Illness, PANSS – Positive and Negative Syndrome Scale, PCR – polymerase chain reaction, SDS – Schedule for the Deficit Syndrome, SNP – single-nucleotide polymorphism, TSH – thyroid-stimulating hormone, Val – valine

Introduction

Seeking for biological background of schizophrenic pathophysiology is essential because of its clinical, therapeutical and pharmacological implications. For decades a variety of concepts of the disease onset, symptoms development together with recognition of factors influencing treatment have been analyzed. Chemical substances (not only medicaments) and their role in changing the course of the disease is also an important aspect of these considerations [5, 8, 32, 41–43, 51].

Schizophrenic process is understood as a whole spectrum of patient's impairment, including social, emotional, cognitive impairment as well as disturbed thought processes. Many patients with schizophrenia suffer from negative primary symptoms, which are not secondary to adverse drug response, depression, social isolation, disintegration or others. This condition is described as deficit syndrome [9]. Although absent in current diagnostic criteria, in ICD-11 negative symptoms will be considered as significant for diagnosing schizophrenia with dominating negative symptoms [47]. Following symptoms with at least two of them, persistent for the preceding 12 months allow the diagnosis: blunted affect, poverty of speech, restricted content of speech, attention disturbances, curbing of interests, alogia, avolition, apathy, diminished social relationships. These symptoms must be present both in exacerbation and remission periods [25]. According to some studies, stability of deficit may be a marker of the clinical form of schizophrenia [1, 15]. A meta-analysis of 47 studies found increased severity of negative symptoms, disorganization symptoms and reduced severity of affective symptoms in a group of patients with deficit schizophrenia. No significant differences in the severity of positive symptoms were found [11]. Estimated incidence of DS is 15% in first-episode schizophrenia, 25–30% in chronic schizophrenia, 14–17% in population studies [26, 27]. Therefore, it is a relatively numerous population which may be an object of targeted and specific therapeutic intervention. Patients with DS showed worse premorbid adjustment [16], poorer quality of life, increased isolation, worse level of functioning [48]. They show lower scores in neuropsychological functioning and those with negative symptoms, dominant in DS, are prone to neurocognitive disorders linked to frontal lobe and parietal lobe dysfunction [12]. Associations were found between the presence of the DS and both summer birth and a family history of schizophrenia. Kirkpatrick confirmed an association between the DS and a family history of schizophrenia [26]. Sibling correlation of the DS was confirmed in a study, in which a positive correlation was found between the DS and a family history of DS [44]. However, there is no proof for the familial resemblance to be due to biological, i.e., hereditary, or environmental factors. There are few findings about potential genetic risk factors in the DS.

Many recently identified genes are potential risk factors in schizophrenia. One of them is a gene of the brain-derived neurotrophic factor (BDNF). BDNF gene is localized on chromosome 11 (11p13) [33]. BDNF is a protein engaged in neuronal plasticity process [3] and also plays a role as a mediator in behavioral interactions between organism and environment [31]. It is involved in the mechanisms of serotonergic, dopaminergic, noradrenergic neurotransmission and it might be responsible for triggering schizophrenia [20] and comorbid cognitive impairments [14]. It is also studied in affective disorders [38] and addictions [19]. Antipsychotic treatment regulates levels of BDNF in the brain, thus, regulation of neurotrophic factors could be a crucial factor in psychiatric treatments [2].

Another crucial factor in schizophrenic background analysis is an enzyme catechol-O-methyltransferase (COMT), which is involved in the degradation of dopamine. COMT gene is located on chromosome 22 (22q11). This is a functional polymorphism: valine-to-methionine (Val/Met) substitution, which results respectively in low activity form of the enzyme (Met variant) [28]. Polymorphisms of the COMT gene may also play a role in schizophrenia. Both the presence and the lack of perceptible associations were observed in schizophrenia populations [22], some researchers found a link between COMT polymorphisms and cognitive impairments [13, 30] as well as negative symptoms of schizophrenia [29]. Because the clinical picture conditioned by polymorphisms of the above mentioned genes may play a role in the development of the disease-related phenotypes, their analysis has been conducted in the present study.

The aim of the study was to assess a potential association of the investigated polymorphisms of the BDNF and COMT genes with the deficit syndrome in schizophrenia.

Methods

All subjects were informed about the aims and the protocol of the study and gave their written informed consent. The protocol was approved by the Bioethics Committee of the Pomeranian Medical University of Szczecin.

The obtained data were analyzed to conduct genetic analysis of the polymorphisms of the BDNF (Val66Met) rs6265 and COMT (Val158Met) rs4680 genes.

Control group: consisted of 100 somatically and mentally healthy Caucasian subjects of Polish origin matched for ethnicity, sex and age (56 men and 44 women), average age of 36.18 ± 11. All interviewees with suspected mental disorders were excluded from further studies. Subjects with psychiatric records (hospitalization or outpatient care) and psychoactive substances abuse (excluding nicotine or caffeine) were also eliminated from the study [39].

Investigated group: consisted of 110 male and 90 female Caucasian unrelated subjects at an average age of 39 ± 10.4. All patients were treated according to Polish standards of schizophrenia treatment and followed recommendations [23]. The group consisted of inpatients and outpatients. At the time of examination all patients were stabilized (no acute psychosis).

Inclusions criteria: aged 18–60, diagnosed with paranoid schizophrenia according to ICD-10 [36], ability to understand the study procedures, informed consent for participation in the study, schizophrenia diagnosis present at least 18 months.

Exclusion criteria: other mental diseases, dementia or significant organic brain injury, epilepsy, alcohol addiction or substance abuse, poor somatic health (carcinoma, cardiovascular illnesses, diseases of respiratory, gastrointestinal, excretory systems, hormone disorders).

To make objective the somatic health of the subjects, the following biochemical blood tests were conducted: complete blood count, blood glucose level tests, TSH, AST, ALT, ionogram, urea level, creatinine level. The test results of patients qualified for the study were within laboratory normal ranges.

The above exclusion criteria were supposed to help in drawing more precise conclusions after selecting a group of patients with deficit schizophrenia, i.e., to minimize the possible influence of other, organic mental disorders.

Questionnaires and scales: additional data about the patients were obtained through demographic data questionnaires, OPCRIT (Operational Criteria for Psychotic Illness) [34], MINI (Mini International Neuropsychiatric Interview) [45] and psychometric scales: PANSS (Positive and Negative Syndrome Scale) [24], SDS (Schedule for the Deficit Syndrome) – to rate negative symptoms in deficit [25].

Deficit (DS) and nondeficit (NDS) subgroups of patients

According to Carpenter's concept [9] and using a proper research instrument – Schedule for the Deficit Syndrome (SDS) [25], and regarding subjects' clinical symptoms, medical history, and social functioning impairment, the cohort was divided into 2 subgroups:

1. patients with schizophrenia with the deficit syndrome – deficit schizophrenia (DS) n = 81; female subjects n = 28, male subjects = 53;
2. patients with schizophrenia without the deficit syndrome – nondeficit schizophrenia (NDS) n = 119; female subjects n = 61, male subjects n = 58.

Statistical analysis

Data on family, social, professional, etc. functioning was analyzed in both subgroups. The χ^2 test was used to analyze statistical relationships of nonlinear variables and to calculate differences in the frequency of genotypes and alleles. Results were considered statistically significant for $p < 0.05$.

Genetical analysis

Genetical analysis was conducted using real time PCR and LightCycler 2.0 (Roche Diagnostics) according to the Methodology from Quality Control Guidelines of Laboratory of Psychiatric Genetics at the Pomeranian Medical University. The following SNPs were analyzed:

– BDNF rs6265 Ex11 Val66Met 11p13; the melting temperature for the G (Val) allele Tm = 56.94[°C]; for the A (Met) allele Tm = 62.83[°C];
– COMT rs4680 Ex5 Val158Met 22q11.2t; the melting temperature for the G (Val) allele Tm = 58.43[°C]; for the A (Met) allele Tm = 64.67[°C].

Results

There were no statistically significant differences between DS and NDS groups pointing out to the presence of potentially harmful family, social and environmental factors.

Genetic analysis results – Hardy-Weinberg's equilibrium was maintained in the total investigated group.

In the analyzed group we found no statistically significant differences between the genotype and allele frequencies of the BDNF gene rs6265 polymorphism and the COMT gene rs4680 polymorphism in the whole group of patients with schizophrenia compared to the control group, as well as regarding the gender of studied patients (Tab. 1).

Likewise, no differences were found between the alleles and genotype frequencies of the BDNF gene rs6265 polymorphism and the COMT gene rs4680 polymorphism in the DS subgroup compared to the control group (Tab. 2) and in the NDS subgroup compared to the control group (Tab. 3).

As gender-related analysis showed no differences – its outcomes are not presented in the paper.

We found statistically significant differences between the genotype frequencies of the COMT gene rs4680 polymorphism: more homozygous Val/Val were found (31 *vs.* 17%; p = 0.027) in the NDS compared to the DS subgroup. In DS group we found also more homozygous Met/Met than Val/Val (31 *vs.* 17%).

There were no statistically significant differences between the genotype and allele frequencies of the BDNF gene rs6265 polymorphism between the DS and NDS subgroups.

Analyses regarding gender for both genes showed no differences – data were not included in the tables.

Discussion

The analysis of the obtained data found no significant differences in the factors linked to perinatal, early

Tab. 1. Frequency of the genotypes and alleles of the polymorphisms of the BDNF gene (rs6265) and the COMT gene (rs4680) in the control and in patients with schizophrenia

Polymorphism BDNF rs 6265 Val66Met (G/A)										
				Genotypes				Alleles		
Groups	n	Gender	HWE	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
SCHI	194	MF	0.42	136 (70)	51 (26)	7 (4)	0.61	323 (83)	65 (17)	0.31
Control	96	MF	0.83	72 (75)	22 (23)	2 (2)		166 (86)	26 (14)	
SCHI	108	M		77 (71)	27 (25)	4 (4)	0.79	181 (84)	35 (16)	0.58
Control	54	M		40 (74)	13 (24)	1 (2)		93 (86)	15 (14)	
SCHI	86	F		59 (69)	24 (28)	3 (3)	0.67	142 (83)	30 (17)	0.37
Control	42	F		32 (76)	9 (21)	1 (3)		73 (87)	11 (13)	
Polymorphism COMT rs 4680 Val158Met (G/A)										
				Genotypes				Alleles		
Groups	n	Gender	HWE	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
SCHI	194	MF	0.05	49 (25)	82 (42)	63 (32)	0.43	180 (46)	208 (54)	0.71
Control	100	MF	0.99	23 (23)	50 (50)	27 (27)		96 (48)	104 (52)	
SCHI	106	M		25 (24)	47 (44)	34 (32)	0.78	97 (46)	115 (54)	0.56
Control	56	M		14 (25)	27 (48)	15 (27)		55 (49)	57 (51)	
SCHI	88	F		24 (27)	35 (40)	29 (33)	0.38	83 (47)	93 (53)	0.93
Control	44	F		9 (20)	23 (52)	12 (27)		41(47)	47 (53)	

SCHI – patients with schizophrenia, Val – valine, Met – methionine, G – guanine, A – adenine, M – male, F – female

Tab. 2. Frequency of genotypes and alleles of the polymorphisms of the BDNF gene (rs6265) and the COMT gene (rs4680) in the control and in patients with deficit schizophrenia (DS)

Polymorphism BDNF rs 6265 Val66Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
DS	78	MF	56 (72)	21 (27)	1 (1)	0.77	133 (85)	23 (15)	0.74
Control	96	MF	72 (75)	22 (23)	2 (2)		166 (86)	26 (14)	
Polymorphism COMT rs 4680 Val158Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
DS	78	MF	13 (17)	41 (53)	24 (31)	0.56	67 (43)	89 (57)	0.34
Control	100	MF	23 (23)	50 (50)	27 (27)		96 (48)	104 (52)	

DS – patients with deficit schizophrenia, Val – valine, Met – methionine, G – guanine, A – adenine, MF – male and female

Tab. 3. Frequency of genotypes and alleles of the polymorphisms of the BDNF gene (rs6265) and the COMT gene (rs4680) in the controls and in patients without deficit schizophrenia (NDS)

Polymorphism BDNF rs 6265 Val66Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
NDS	116	MF	80 (69)	30 (26)	6 (5)	0.41	190 (82)	42 (18)	0.20
Control	96	MF	72 (75)	22 (23)	2 (2)		166 (86)	26 (14)	
Polymorphism COMT rs 4680 Val158Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
NDS	116	MF	36 (31)	41 (35)	39 (34)	0.91	113 (49)	119 (51)	0.88
Control	100	MF	23 (23)	50 (50)	27 (27)		96 (48)	104 (52)	

NDS – patients without deficit schizophrenia, Val – valine, Met – methionine, G – guanine, A – adenine, MF – male and female

childhood, school periods, exposure to alcohol and tobacco smoke in the prenatal period, a family history of mental and neurological diseases that could trigger the development/manifestation of the deficit syndrome in the course of schizophrenia.

The literature contains little data on the analysis of genetic factors of the deficit syndrome in schizophrenia. Our study did not reveal differences in genotype and allele frequencies of the investigated BDNF gene polymorphisms between the investigated group of patients with schizophrenia and the controls, nor between the subgroup of patients with the deficit syndrome and the subgroup without the syndrome. Contrary to our findings, Neves-Pereira et al. [37] on a Scottish population found an association between Val allele of the BDNF gene polymorphism and the presence of schizophrenia. However, Spalletta et al. [46], in a study on a population of Italian patients, did not find that an allele of the BDNF gene polymorphism was associated with negative, general and positive symptoms measured with PANSS, which is in line with our finding and which was replicated by Naoe et al. [36].

The COMT Val158Met polymorphism investigated in present study is linked to the presence of schizo-

phrenia. Meta-analysis of genome-wide linkage studies identified chromosome 22q (with COMT gene) as loci to be candidate for a schizophrenia research [4]. Our analysis of the COMT polymorphism revealed no differences in allele and genotype frequencies in the whole group of schizophrenia patients *vs.* controls. This result is in line with a meta-analysis conducted by Munafo et al. [35], who also did not confirm an association between Val158Met polymorphism and schizophrenia as well as with Tybura et al. (Polish population) [50], Tovilla-Zárate et al. (Spanish population) [49] and in Chinese population – Zhang et al. [54] results. Galderisi et al. delivered similar results to ours, showing no associations between the above polymorphisms and schizophrenia. They stated also, that the COMT Val158Met polymorphism influences executive functions in schizophrenia and the neuromotor performance in the deficit subtype only [17, 18]. There is evidence that the existence of a haplotype, containing Val allele, can trigger development of schizophrenia, although the presence of Val allele itself cannot simply be equated with an increased risk of disease. Chen et al. confirmed that observation, noticing lower presence of persons with Val allele haplotype among schizophrenic patients [10]. These results are in line with our observations on genotype differences between DS and NDS. Wonodi et al. [53] found differences in the frequencies of the COMT Val158Met polymorphism between patients with schizophrenia and the control group, confirming our findings. They did not observe any differences in allele and genotype frequencies between a group of probands with deficit and nondeficit forms of schizophrenia, which is not consistent with our findings – we found differences between deficit and nondeficit forms of schizophrenia – in DS group less homozygous Val/Val and more heterozygous Val/Met were found. Such differences were not observed in NDS group (Tab. 4). The Wonodi's sample consisted of 136 European-American subjects (51 female, 85 male), the DS group consisted of 1 woman and 20 men, NDS group – 28 women, 37 men. Our groups were larger : DS – female subjects n = 28, male subjects n = 53; NDS – female subjects n = 61, male subjects n = 58 and controls n = 100. In genetic analysis gender and number has inevitable influence on results. Differences in our and Wonodi's observations are probably due to this fact. Badner analyzed a claim that the Met allele would elevate the susceptibility to schizophrenia [4]. The hypothesis that more severe/chronic schizophrenia may be associated with Met and milder forms of schizophrenia with the Val allele is supported by Herken and Erdal [21]. They stated that the Met allele is associated with higher severity of symptoms (measured by the BPRS) and with more frequent hospitalization. Bilder et al. [6] reported that more severe symptoms of schizophrenia (negative symptoms) are associated with the Met allele, despite the observation in the same study that the Met allele was associated with better performance on neurocognitive tests. Data presented above are confirmative to our results. Our DS subgroup showed significantly lower

Tab. 4. Frequency of genotypes and alleles of the polymorphisms of the BDNF gene (rs6265) and the COMT gene (rs4680) in patients with deficit schizophrenia (DS) and in patients without deficit schizophrenia (NDS)

Polymorphism BDNF rs 6265 Val66Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
DS	78	MF	56 (72)	21 (27)	1 (1)	0.36	133 (85)	23 (15)	0.77
NDS	116	MF	80 (69)	30 (26)	6 (5)		190 (82)	42 (18)	
Polymorphism COMT rs 4680 Val158Met (G/A)									
			Genotypes				Alleles		
Groups	n	Gender	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	p	Val	Met	p
DS	78	MF	13 (17)	41 (53)	24 (31)	0.027	67 (43)	89 (57)	0.26
NDS	116	MF	36 (31)	41 (35)	39 (34)		113 (49)	119 (51)	

DS – patients with deficit schizophrenia, NDS – patients without deficit schizophrenia, Val – valine, Met – methionine, G – guanine, A – adenine, MF – male and female

occurrence of the Val/Val genotype compared to NDS subgroup. The course of the disease in deficit patients is much more severe, their quality of life lower and general mental health and functioning assessment worse than in patients without the deficit syndrome. Bilder stated: it can be hypothesized that the Met allele may be associated with a vulnerability to the schizophrenia syndrome that is characterized by negative symptoms and pathologic inflexibility, while the Val allele may be associated with a form of the syndrome prone to show positive symptoms, reactive disorganization and hyperarousal to what are usually innocuous stressors [7], which again is confirmative to our observations. On the basis of Chinese population of Han, Wang reported that haplotypes of rs4633(C)-rs4680(Met) COMT polymorphisms were significantly associated with four of the seven individual negative symptoms: blunted affect, emotional withdrawal, poor rapport and passive social withdrawal [52]. We observed twice as much Met genotypes than the Val ones in our DS group, which is consistent with above cited study.

The differences observed in genotypes distribution in our group may be the result of slightly different genetic background of deficit syndrome, which supports the above mentioned concept of DS endophenotype in schizophrenic group.

Although the size of the investigated group (200 patients) inevitably constitutes a substantial limitation of the present study, further research on a larger cohort is under way. The important positive element of the study is the moment of clinical assessment – the symptomatology of the investigated patients was at a low level, all patients were stabilized, without acute psychosis. Consequently, the reliability of the obtained data seems to be satisfactory.

Conclusions

The analysis of the COMT rs4680 polymorphism in the present DS and NDS study shows that some genetic factors may be relevant in analyzing the reasons for the differentiation of schizophrenic subtypes Differences in genotype distribution among several phenotypes of schizophrenia may be, following a replication study, the basis for an attempt of isolating a deficit endophenotype of schizophrenia.

The BDNF gene rs6265 polymorphism analysis does not support the speculations about its influence on the incidence of schizophrenic subtypes.

Competing interests:
The authors declare that they have no competing interest.

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