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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.

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