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Disorganization at the stage of schizophrenia clinical outcome: Clinical–biological study

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ABSTRACT

Background: According to the multidimensional model of schizophrenia, three basic psychopathological dimensions constitute its clinical structure: positive symptoms, negative symptoms and disorganization. The latter one is the newest and the least studied. Our aim was to discriminate disorganization in schizophrenia clinical picture and to identify its distinctive biological and socio-psychological particularities and associated genetic and environmental factors.
Methods: We used SAPS/SANS psychometrical scales, scales for the assessment of patient's compliance, insight, social functioning, life quality. Neuropsychological tests included Wisconsin Card Sorting Test (WCST), Stroop Color-Word test. Neurophysiological examination included registration of P300 wave of the evoked cognitive auditory potentials. Environmental factors related to patient's education, family, surrounding and nicotine use, as well as subjectively significant traumatic events in childhood and adolescence were assessed. Using PCR we detected SNP of genes related to the systems of neurotransmission (*COMT*, *SLC6A4* and *DRD2*), inflammatory response (*IL6*, *TNF*), cellular detoxification (*GSTM1*, *GSTT1*), DNA methylation (*MTHFR*, *DNMT3b*, *DNMT1*).
Results: Disorganization is associated with early schizophrenia onset and history of psychosis in family, low level of insight and compliance, high risk of committing delicts, distraction errors in WCST, lengthened P300 latency of evoked cognitive auditory potentials, low-functional alleles of genes *MTHFR* (rs1801133) and *DNMT3b* (rs2424913), high level of urbanicity and psychotraumatic events at early age.
Conclusions: Severe disorganization at the stage of schizophrenia clinical outcome is associated with the set of specific biological and social–psychological characteristics that indicate its epigenetic nature and maladaptive social significance.

1. Introduction

Disorganization represents relatively new concept in psychiatry, reflecting the advanced trends of modern schizophrenia taxonomy, which are based on the methods of mathematical modeling and have replaced the outdated categorical approach with the simplified splitting of the clinical picture into "positive" and "negative" symptoms [1]. It manifests with disturbed behavior (eccentricity, mannerisms, paradoxical acts, aggression, agitation, rituals and stereotype actions) and "positive formal thought disorders" – distortion of thinking with inconsistency, disrupted speech, tangentiality and agrammatical construction of phrases. Marked social importance of disorganization syndrome is explained by the fact that disturbed behavior often takes the form of illegal acts, while incoherent thinking and speech make it almost impossible to establish productive contact between doctor and

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patient and can "mask" delusions and hallucinations (including imperative "voices" convincing the patient to commit suicide).

Disorganization remains the least studied of the three psychopathological dimensions of schizophrenia. Results of the relevant clinical–biological studies have low reproducibility and are not consolidated within a single concept. Genetic markers of disorganization have been established in only few studies: association was found with loci 6p21, 6q11.2–6q14.2, 20q11, 9pter [2], 22q11 [3] and polymorphism of gene *DRD2* Ser/Cys 311 [4]; other studies failed to find any significant linkage [5]. Data on environmental determinants of disorganization is even more rare. M. Cancel with colleagues have shown that disorganization is associated with childhood neglect [6].

Differentiated pathogenesis-based treatment strategy for schizophrenia patients with severe disturbances of thinking and behavior has not still been developed. Moreover, there is a confounding factor: disorganization has been analyzed by researchers at different stages of schizophrenia, although the disease symptom profile is undergoing significant changes and reaches relative consolidation only at the stage of the clinical outcome (12–15 years after its clinical debut) [7]. Comprehensive study of disorganization at the stage of schizophrenia clinical outcome is needed involving clinical–biological, social and psychological correlates, environmental and genetic determinants, that will provide the deeper understanding of its nature and create theoretical basis for its differentiated prevention and treatment. Thus, objective of our study is to identify the distinctive clinical–biological and socio-psychological features of disorganization syndrome and its predisposing factors.

2. Material and methods

The study design was clinical–biological, observational-analytical, cross-sectional; case–control; when collecting the anamnestic data the clinical-anamnestic method was used.

2.1. Object of the study

18–65 years old patients with schizophrenia undergoing the course of treatment in the Republican research and practice center for mental health (Minsk). Written informed consent was obtained from all patients, its form has been approved by the ethic committee of the Republican research and practice center for mental health. Patients' privacy rights were complied with.

2.2. Inclusion criteria

Verified diagnosis "schizophrenia" (in accordance with the ICD-10 criteria); age 18–65 years; disease duration (since the primary manifestations of psychotic symptoms) – 12 years or more; written informed consent to participate in the study.

2.3. Exclusion criteria

Decompensated somatic illness; neurological disturbances and prominent extrapyramidal symptoms (total Extrapyramidal Symptoms Rating Scale score >11); comorbidity with other mental disorders; psychoactive substance intoxication; systematic use of antipsychotics during 3 weeks prior to the hospital admission (in order to minimize the effect of neuroleptics on disorganization); pregnancy; low incapacity.

During the first stage of the study, 800 subjects with the verified diagnosis "schizophrenia" have been randomly selected among the patients of the Republican research and practice center for mental health (with the use of the "random number generator" application). During the second stage of the study, only those patients who met the inclusion criteria for the study were left in the sample ($n = 336$). After comprehensive examination of patients and collecting statistical data, the sample was spitted into two comparison groups based on the sum of the global SAPS scores for disorganization dimension: patients with severe disorganization syndrome (score ≥7.5 – *main group*) ($n = 73$) and patients without severe disorganization syndrome (score <7.5 – *comparison group*) ($n = 263$). Additional comparison groups were formed based on the severity of each of 2 symptoms of disorganization (behavioral disturbances and positive formal thought disorders): with severe symptom (SAPS global score ≥3 – *main group*) and without severe symptom (SAPS global score <3 – *comparison group*), as well as each of the 12 signs of SAPS disorganization dimension: with severe sign (SAPS score ≥3 – *main group*) and without severe sign (SAPS score <3 – *comparison group*). The following disorganization signs were assessed: bizarre clothing and appearance, bizarre social and sexual behavior, aggressive behavior and agitation, repetitive or stereotyped behavior, derailment, tangentiality, incoherence, illogicality, circumstantiality, logorrhea, distractibility, clanging (association by consonance).

To assess the clinical picture of schizophrenia we used psychometrical scales SANS, the Scale for the Assessment of Negative Symptoms (N. Andreasen, 1983), SAPS, the Scale for the Assessment of Positive Symptoms (N. Andreasen, 1984). The sign "inattentiveness" was not assessed as we used more informative cognitive tests for that purpose. Formal thought disorders, delusions and hallucinations were evaluated in the "worst" state of patient within the first days of his/her hospitalization. Emotional flattening and speech poverty were assessed only after extremely severe positive symptoms were corrected within the next few days, so that too "bright" symptoms did not interfere with the interview and could not disguise less prominent negative symptoms. Apathy–abuly, anhedonia–asociality and behavioral abnormalities were assessed in the "best" state when patient reported to be ready for discharge and included retrospective analysis of his/her life prior to hospitalization.

To assess socio-psychological characteristics of schizophrenia we used the Scale for the assessment of compliance (K. Kemp, G. Kirov, B. Everitt et al., 1998), Scale to assess unawareness of mental disorder (X. F. Amador), Scale for the evaluation of patient's functioning defect in different social spheres, Brief questionnaire of the WHO to assess the quality of life (WHOQOL-BREF). To measure neurological abnormalities caused by neuroleptics we used Extrapyramidal Symptoms Rating Scale, ESRS-A (Chouniard/Alphs, 2004).

Neuropsychological tests included Wisconsin Card Sorting Test (WCST), Stroop Color-Word test. Neurophysiological examination was carried out with the use of the computer multifunctional complex "Нейро-МВП-4" with the registration of the late positive P300 wave of the evoked cognitive auditory potentials of the brain.

The following environmental factors were registered: patient's education, social status of his/her parents, rising up in complete/incomplete family, urbanicity, long-term regular use of nicotine (every day during 10 years or more), subjectively significant traumatic events in childhood and adolescence (parental divorce, living in a boarding house/colony for minors, upbringing without parents or by single-parent, death of the close family member, physical abuse, sexual abuse, emotional abuse, bullying at school, serious illnesses/injuries/surgery). Information was obtained from the interview with patients and their relatives prior to discharge.

Polymerase chain reaction was performed to determine the single nucleotide polymorphism of genes related to the following systems: neurotransmission (*COMT* rs4680, *SLC6A4* 5HTTLPR and *DRD2* rs1800497), inflammatory response (*IL6* rs1800795, *TNF* rs1800629), cellular detoxification (*GSTM1*, *GSTT1* deletions), DNA