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

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A R T I C L E   I N F O
Article history:
Received 11 December 2016
Accepted 16 December 2016
Available online 30 December 2016

Keywords:
Schizophrenia
Disorganization
Environmental
Genetic
Methylation
Epigenetics

A B S T R A C T

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. Neuropsychological 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.

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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...
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 split 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, clinging (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–abulys, 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. Evertt 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. Neuropsychological examination was carried out with the use of the computer multifunctional complex “Heiho-MBTI-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, SLCA4 SHTTLP and DRD2 rs1800497), inflammatory response (IL6 rs1800795, TNF rs1800629), cellular detoxification (GSTM1, GSTT1 deletions), DNA
methylation (\textit{MTHFR} rs1801133, \textit{DNMT3b} rs2424913, \textit{DNMT1} rs2228612).

Statistical calculations were performed with the use of the following computer statistics instruments: SPSS 13.0, GPower, WinPepi.

### 3. Results and discussion

Analysis of the data obtained has shown that disorganization is present in the majority of cases of schizophrenia at the stage of its clinical outcome (93.5%). Its severity varies from the mild manifestations (22.5%) up to the critical values (21.9% of cases) (Fig. 1); most of its characteristics are evident for the researcher (SAPS score 3 and higher), and its most prominent manifestations are represented by behavioral disturbances (severe in 70.8% of cases). In vast majority of cases (98.5%) patients were diagnosed with “paranoid schizophrenia” (F20.0) regardless of the severity of disorganization.

Confirmatory factor analysis was performed at the level of 48 schizophrenia signs of SAPS/SANS scales (the method of extracting factors – principal component analysis, the method of rotation – Varimax). The scree plot diagram made it possible to identify three main factors explaining 42.3% of the total dispersion of the variables (Fig. 2).

Analysis of the rotated component matrix confirmed that disorganization represents the autonomic and independent psychopathological phenomenon along with the positive (delusions, hallucinations) and negative (emotional flattening, poverty of speech, apathy, abuly, anhedonia–asociality) symptoms of schizophrenia.

Correlation analysis has shown the absence of statistically significant association of disorganization symptoms with positive symptoms of schizophrenia and only weak negative relationship with negative symptoms (Table 1).

The total number of patients with severe disorganization was 73 (31 females, 42 males), they did not differ significantly from the comparison group by gender and age ($P > 0.05$).

Patients with severe disorganization did not differ from the comparison group by the severity of most of the accompanying schizophrenia symptoms, but had significantly lower severity of anhedonia–asociality ($P = 0.046$). Patients with prominent bizarre behavior and positive formal thought disorders (global SAPS score $\geq 3$) differed from the rest of the sample by significantly less severe affective flattening (respectively, $P = 0.013$) and apathy–abuly ($P = 0.017$), anhedonia–asociality ($P = 0.007$) which indicates the relatively preserved motivational and volitional resources required for maladaptive behavior manifestations.

Patients with severe disorganization were significantly less likely to be employed ($P = 0.013$) and to be engaged in marriage ($P = 0.033$) compared to the rest of the sample. Schizophrenia debut has occurred significantly earlier in that group of patients compared to the other subjects ($P = 0.005$) including the cases of disease onset under the age of 20 ($OR = 1.92; 95\% CI 1.43–2.58$). Severity of the other clinical dimensions of schizophrenia (positive, negative symptoms) did not show significant linkage with the age of the disease onset ($P > 0.05$).

Patients with severe disorganization were significantly more likely to commit delicts than the rest of the subjects ($OR = 2.19; 95\% CI 1.63–2.94$) as well as the crimes accompanied by the criminal charges and/or use of coercive measures of security and treatment ($RR = 2.84; 95\% CI 1.52–5.31$). These differences were not observed between the groups of patients differed by the severity of positive and negative symptoms ($P > 0.05$).

Analysis of the Wisconsin Card Sorting Test (WCST) performance has shown that patients with severe disorganization were significantly more likely to commit “distraction errors” ($P = 0.012$) compared to the rest of the sample. This type of error occurs when the subject is not able to follow the card sorting algorithm and makes decisions at random not considering the given test conditions and their personal classification experience in the previous categories.

Indicators of the Stroop Color-Word test did not differ significantly between the two comparison groups ($P > 0.05$).

Patients with severe disorganization had significantly higher sum score on the Scale to assess unawareness of mental disorder compared to the other subjects ($P = 0.001$). These differences were not observed between the groups of patients differed by the

<p>| Table 1 Correlation analysis of schizophrenia SAPS/SANS symptoms global scores. |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>SAPs symptoms</strong></th>
<th><strong>Bizarre behavior</strong></th>
<th><strong>Formal thought disorders</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>$r = -0.083$; $P = 0.129$</td>
<td>$r = -0.056$; $P = 0.309$</td>
</tr>
<tr>
<td>Delusions</td>
<td>$r = 0.064$; $P = 0.244$</td>
<td>$r = 0.139$; $P = 0.011$</td>
</tr>
<tr>
<td>Bizarre behavior</td>
<td>$r = 1.000^*$; $P = 0.000$</td>
<td>$r = 0.435^*$; $P = 0.000$</td>
</tr>
<tr>
<td>Formal thought disorders</td>
<td>$r = 0.435^*$; $P = 0.000$</td>
<td>$r = 1.000^*$; $P = 0.000$</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>$r = -0.150^*$; $P = 0.006$</td>
<td>$r = -0.136^*$; $P = 0.013$</td>
</tr>
<tr>
<td>Speech poverty (alologia)</td>
<td>$r = -0.053$; $P = 0.333$</td>
<td>$r = 0.124^*$; $P = 0.023$</td>
</tr>
<tr>
<td>Apathy–abuly</td>
<td>$r = -0.114^*$; $P = 0.037$</td>
<td>$r = -0.178^*$; $P = 0.001$</td>
</tr>
<tr>
<td>Anhedonia–asociality</td>
<td>$r = -0.187^*$; $P = 0.001$</td>
<td>$r = -0.153^*$; $P = 0.005$</td>
</tr>
</tbody>
</table>

*Note: Spearman correlation coefficient ($r$) and the corresponding level of significance are displayed. The * indicates statistically significant differences.*
severity of positive and negative symptoms of schizophrenia ($P > 0.05$). Considering the fact that the higher is the overall score on the insight assessment scale, the lower is the measured value (awareness of the disease), we can conclude that disorganization is associated with reduced patient's awareness of his/her own disease and the lack of the critical evaluation of the actions made (including aggressive ones) as the result of thinking process violations.

Patients with severe disorganization had significantly lower sum score on the Scale for the assessment of compliance compared to the other subjects ($P = 0.043$). These differences were not observed between the groups of patients differed by the severity of positive and negative symptoms of schizophrenia ($P > 0.05$). That confirms the statement that it is the disorganization that impedes the cooperation between patient and doctor and prevents the establishment of productive therapeutic relationships.

The total score of the WHO questionnaire of life quality and the total score of the Scale for the evaluation of patient's social functioning defect did not show any significant differences between disorganization comparison groups ($P > 0.05$). Lower scores on these instruments were associated with more severe negative symptoms ($P < 0.05$).

The latency of P300 wave of the evoked cognitive auditory potentials and its elongation relative to the upper limit of the age norm were significantly higher in patients with severe positive formal thought disorders ($P = 0.006$) as well as in patients with severe speech poverty ($P = 0.024$) compared to the rest of the sample, reflecting the delayed processing of the auditory information in the brain. These characteristics of P300 wave were not peculiar to the individuals who differed by the severity of positive and negative schizophrenia symptoms ($P > 0.05$).

Analysis of the environmental factors has shown that severe disorganization is associated with the long-term living in highly urbanized areas with more than 1.5 million of inhabitants (OR = 3.38; 95% CI 2.88–3.96). The probability of living in the large densely populated city is more than 1.5 times higher in patients with severe aggression (OR = 1.67; 95% CI 1.19–2.34) and more than 3 times higher in those with severe repetitive behavior (OR = 3.37; 95% CI 1.28–8.86). Modifying influence of the urbanicity on schizophrenia clinical picture can be explained by its association with the high level of noise, narrow personal space boundaries, abundance of the interpersonal contacts, high pace of life that allows us to consider it as the non-specific stressor causing the long-term morphofunctional "restructuring" of the central nervous system.

Analysis of the environmental factors distribution at the level of 12 signs of disorganization according to the SAPS scale has revealed additional relationships (Fig. 3). The probability of having only basic (9 years) education or no education at all is almost 2 times higher in patients with severe thought disorders (tangentiality (OR = 1.72; 95% CI 1.16–2.56), distractibility (OR = 2.10; 95% CI 1.22–3.63)) and almost 3 times higher in patients with severe aggression (OR = 2.92; 95% CI 2.13–4.01). Modifying influence of the low education level on the clinical picture of schizophrenia can be explained by the lack of the systematic cognitive training and the lack of the formal socialization of individual in a team which usually promotes the development of social intellect as well as the range of adaptive skills including conscious control over the biological impulses, frustration overcoming, delayed gratification. However, incomplete education may be also the result of the specific traits related to premorbid functioning and clinical debut of the studied schizophrenia variants.

The probability of having suffered from the traumatic events at young age (<18 years old) is almost 2 times higher in patients with severe aggressive behavior/agitation (OR = 1.96; 95% CI 1.31–2.93). Patients with severe disorganization were significantly more common to report the parental divorce under the age of 18 (OR = 2.49; 95% CI 1.40–4.42). Thus, the loss of family integrity and separation from the parent, subjectively experienced by the individual as severe traumatic event, are more important for the formation of severe disorganization in schizophrenia clinical structure than negative experience related to physical suffering or social rejection.

Analysis of the genetic factors has shown that none of the studied genes related to the systems of cell detoxification, pro-inflammatory response or dopaminergic/serotoninergic neurotransmission have significant association with severe signs of disorganization. At the same time the results indicate the association of severe disorganization with the low-functional T allele of the locus rs1801133 of gene coding the methionine synthesis enzyme methylenetetrahydrofolate reductase MTHFR (OR = 1.91; 95% CI 1.53–2.40). The probability of T allele presence is 2–3 times higher in subjects with severe positive formal thought disorders: derailment (OR = 2.27; 95% CI 1.52–3.37), tangentiality (OR = 2.29; 95% CI 1.41–3.71), illogilicity (OR = 1.93; 95% CI 1.45–2.55), circumstantiality (OR = 3.31; 95% CI 1.75–6, 23), speech pressure (OR = 3.04; 95% CI 1.60–5.78) (Fig. 4). Genetically determined reduction in the activity of methionine synthesis enzyme MTHFR in one-carbon cycle is known to cause the accumulation of homocysteine in brain [8] which is able to...
activate NMDA glutamate receptors [9] shifting the balance between the excitatory and inhibitory neurotransmission in CNS.

Analysis of genetic factors distribution in groups of patients with different severity of 12 SAPS signs of disorganization has revealed additional linkages (Fig. 4). Probability of having the family history of psychotic disorders is almost 2 times higher in schizophrenia patients with severe bizarre social/sexual behavior (OR = 1.83; 95% CI 1.04–2.24). This suggests that the innate constitutional features which are heritable may predispose to manifestations of the rough instinctively triggered types of behavior in schizophrenia aimed at basic biological needs satisfaction regardless the situational context and possible consequences.

The probability of combination of the low functional allele T of rs1801133 locus of MTHFR gene and the allele C of rs2424913 locus of gene coding methylation enzyme DNA methyltransferase 3b (DNMT3b), interpreted as the genetically determined DNA hypomethylation, is more than 2 times higher in schizophrenia patients with severe circumstantiality (OR = 2.77; 95% CI 1.59–4.80), speech pressure (OR = 2.31; 95% CI 1.30–4.08), distractibility (OR = 2.13; 95% CI 1.17–3.88) and 1.5 times higher in case of severe derailment (OR = 1.79; 95% CI 1.24–2.59) and illogicality (OR = 1.72; 95% CI 1.31–2.24). Since the process of DNA methylation refers to the basic molecular mechanisms of gene expression regulation, the interpretation of the relationship found is rational to carry out in the context of the epigenetic approach. Given the key role of DNA methylation in coordination of the functional activity of cell assemblies [10] as well as its relatively high level in the central nervous system [11], it can be assumed that the result of genetically determined reduction of activity of methionine synthesis enzyme MTHFR and main embryogenesis methylating enzyme DNMT3b is genome hypomethylation, inefficient establishment of repressive epigenetic modifications, important for the normal CNS maturation, long-lasting uncontrollable increase of gene expression level in brain cells and functional discoordination of the neural networks. That complies with the “miswiring” theory of disorganization [12]. Since the regulation of gene expression is the basic mechanism of adaptation of the organism to the adverse effects of the environment, it can be assumed that individuals with genetically determined decrease in the activity of DNA methylation system are especially vulnerable to adverse exogenous impacts. High level of urbanization and stressful events of early age are able to create the unfavorable “situational afferentation” which leads to establishment of the long-term maladaptive DNA methylation patterns interfering with the natural mechanisms of epigenetic regulation and restricting the organism in its adaptation resources.

4. Conclusions

1. Patients with severe disorganization at the stage of schizophrenic clinical outcome represent the distinct and clinically homogeneous group discriminated by the early disease onset (age under 20 years), family history of psychotic disorders, impaired neuropsychological functioning in executive sphere (distraction errors in WCST), neurophysiological abnormalities (prolonged latency of P300 wave of the evoked cognitive auditory potentials), low insight and low medication compliance during hospitalization in psychiatric hospital as well as high risk of anti-social acts.

2. Environmental factors that increase the likelihood of severe disorganization development at the stage of schizophrenic outcome include: long-term residence in the large urban settlements (over 1.5 million inhabitants) and subjectively significant traumatic events at early age (parental divorce prior to child’s age 18 years).

3. Genetic factors that increase the likelihood of severe disorganization development at the stage of schizophrenia clinical outcome include: the presence of T allele of rs1801133 polymorphic locus of MTHFR gene, and the combination of this T allele of MTHFR gene with allele C of rs2424913 polymorphic locus of DNMT3b gene, interpreted as genetically determined DNA hypomethylation. The linkage of severe disorganization with polymorphism of DNA methylation system genes suggests the involvement of epigenetic mechanisms in the development of this clinical phenomenon. Genes MTHFR and DNMT3b can be considered as “modifier genes” for schizophrenia, the existence of which was suggested by Fanous A. in 2005 [13].

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

Genotyping was performed in the Institute of Genetics and Cytology of the National Academy of Sciences of the Republic of Belarus. This work was supported by the Belarusian Republican Foundation for Fundamental Research of the National Academy of Sciences of the Republic of Belarus [Grant Number M13M-065] provided to the Republican research and practice center for mental health, Minsk.

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