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The Creation of Clinical and Biological Concept of Schizophrenia: Participation of Chronic Inflammation and Genetic Predisposition in the Formation of Psychopathological Disorders

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Summary

The aim of the study was to investigate chronic inflammation and genetic predisposition processes and their contribution to the formation of psychopathological dimensions of schizophrenia and schizophrenia spectrum disorders on the catatonia model. **Method:** the analysis of PubMed/MEDLINE, RSCI and other sources databases on genetics and immunology of catatonia in comparison with the results of our own clinical and biological studies of catatonic disorders as a model of clinical heterogeneity of positive disorders, as well as various mechanisms of their formation. **Results:** the results obtained demonstrate the involvement of inflammatory mechanisms and genetic factors, not associated with the process of inflammation, in the formation of psychopathological disorders in schizophrenia. In accordance with the developed clinical and biological model of schizophrenia, non-specific pathophysiological inflammatory mechanisms determine the development of both positive and negative disorders by different, albeit related, molecular mechanisms. Identification of various psychopathological types of positive disorders (by the example of catatonic disorders) and their comparison with the activity of inflammation allows differentiating these disorders. Such a comparison makes it possible to reveal disorders, that are mainly determined by genetic factors, at the stages of the disease, associated with a low level of inflammation (basic disorders). Positive disorders, mainly determined by inflammatory mechanisms, can probably be considered as less specific, i.e. "secondary" ones. **Conclusion:** within the framework of the developed concept a different ratio of inflammatory mechanisms and genetic ones not assosiated with inflammation, determines the formation of psychopathological disorders and their clinical heterogeneity at various stages of the disease. These disorders represent a broad continuum, at one pole of which there are disorders, determined predominantly by inflammatory mechanisms, and at the other pole by predominantly genetic ones. The activation of inflammation and its attenuation may be one of the variants of a repeatedly recurring cycle of the disease, in which the ratio of inflammatory and genetic mechanisms changes.

Keywords: schizophrenia, positive and negative disorders, inflammation, genetic factors

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INTRODUCTION

Based on the analysis of foreign publications [1–6], as well as the results of clinical and biological studies, conducted at the FSBSI "Mental Health Research Centre" [7–9], the prerequisites for creation of clinical and biological model of schizophrenia were developed.

At the first stage of research in this direction, an attempt was made to establish a connection between the psychopathological characteristics of the basic processual dimensions, i.e. positive and negative disorders, and neurobiological processes (neurochemical, neuromorphological, immunological, biochemical, etc.).

The main conclusion of the first stage of research was the position, that positive and negative dimensions in the psychopathological space of schizophrenia act as independent ones, revealing differentiated functions and their own developmental trajectories, but at the same time, they are interconnected psychopathological formations.

Within the framework of the developed clinical and biological model, the nonspecific pathophysiological process of inflammation (neuroinflammation) is considered as the key one to the formation of these psychopathological dimensions, however, their development is determined by various molecular mechanisms.

During neuroinflammation and activation of microglia increased levels of pro-inflammatory cytokines and neurotoxic molecules are synthesized in the brain.

The imbalance in neurotransmitter systems, associated with the formation of **positive** symptoms, is determined by pro-inflammatory cytokines, which shift tryptophan catabolism towards the kynurenine pathway, while neurotoxic molecules contribute to the neurodegenerative changes, that underlie the development of **negative** symptoms.

The ideas of the differentiated functions of negative/positive disorders concept, laid down at the first stage of research, made it possible to create a new paradigm of the interaction of these basic dimensional structures, which determined not only significant progress in the study of the schizophrenia psychopathology, but also became the basis for the development of new preventive and therapeutic approaches, as well as predictive assessment of disease outcomes. A full details of the first phase research results is presented in the National Manual of Psychiatry [10], as well the as in articles [7, 11–13] and chapters of the monograph [14].

The aim of this study was to investigate (by catatonia model) the processes of chronic inflammation and genetic predisposition, involved in the formation of psychopathological (positive) dimensions of schizophrenia and schizophrenia spectrum disorders.

Method: the analysis of PubMed/MEDLINE, RSCI and other sources databases on genetics and immunology of catatonia in comparison with the results of our own clinical and biological studies of catatonic disorders as a model of clinical heterogeneity of positive disorders, as well as various mechanisms of their formation.

INFLAMMATORY MECHANISMS OF CATATONIC DISORDERS IN SCHIZOPHRENIA

In accordance with the results of the first stage of research on the development of the clinical and biological concept of schizophrenia, inflammation and activation of microglia are the most important pathogenetic link in the formation of catatonic disorders. The involvement of inflammation in the pathophysiology of catatonic disorders in schizophrenia is evidenced, in particular, by an increase in the level of inflammatory markers in the blood of patients with schizophrenia and catatonic disorders detected by various authors. Thus, in the work of F.-C. Zhou et al. [15] it was shown, that the blood of patients with catatonia contains a significantly higher level of C-reactive protein (CRP), one of the highly sensitive markers of systemic inflammation, compared to schizophrenic patients without catatonia. The study also demonstrated, that additional clinical factors that could influence inflammation level, such as body mass index, stress levels, smoking, and comorbidities, did not affect the main result of the study, suggesting that catatonia is associated with higher levels of systemic inflammation. In an earlier study by A.O. Akanji et al. [16], who investigated the association of CRP with clinical phenotypes in Arab patients with schizophrenia, higher levels of CRP in patients with catatonia were also found. A clinical and immunological study of catatonic disorders in schizophrenia and schizophrenia spectrum disorders, conducted at the FSBSI "Mental Health Research Centre", revealed the clinical and immunological heterogeneity of these disorders. Detailed results of these studies were published previously [13]. Thus, it was shown that the selected typological variants of catatonic disorders, i.e. stereotyped and parakinetic catatonia, demonstrated different strength of correlations with the nonspecific pathophysiological process of inflammation.

Parakinetic catatonic disorders were characterized by the lowest level of immune system activation and cellular immunity exhaustion, which was reflected in the assessment of the enzymatic activity of leukocyte elastase, a neutrophil proteolytic enzyme, released into the extracellular space in neutrophil activation due to inflammation. On the contrary, manifestations of stereotyped catatonia were associated with a high level of the immune system activation and a high activity of the proteolytic system of inflammation. The identified clinical and immunological features served as the basis for suggesting an assumption about various molecular mechanisms of these types of catatonic disorders development, associated with different contribution of nonspecific inflammatory mechanisms and genetic mechanisms, not associated with inflammatory processes.

GENETIC MECHANISMS OF CATATONIC DISORDERS IN SCHIZOPHRENIA

The involvement of genetic factors in the development of catatonic disorders is supported by the data of foreign studies in the field of catatonia genetics.

The first studies of hereditarily burdened families, which started in the 30s of the last century, showed that hereditary factors make a significant contribution to the development of catatonia. The authors note, that the phenomenon of anticipation, that is important from a genetic point of view,

takes place in these families, which means growing severity in the course of hereditary diseases from one generation to another [17, 18]. At the beginning of the 21st century, with the development of technologies for studying the genome, it became possible to reveal the sites of chromosomes, associated with disease and transmitted from an affected parent to a child, who also suffers from this disease. Such a region for catatonia was found on the long arm of chromosome 15 (15q15), on chromosome 22 (22q13) and chromosome 4 (4q31) [19–21]. Attempts to map individual genes in these regions have shown that catatonia is associated with the MLC1 membrane protein gene, whose functions are still unknown, but it is assumed that it can perform an integral transmembrane function, transporting ions and molecules of various sizes through biological membranes [22], as well as interleukin 15 receptor antagonist gene (IL-15RA).

A similar mutation of the interleukin gene is also associated with the behavior of mice phenotypically close to catatonia in experimental models [21]. Experimental models have also shown that the CNP 2′,3′ gene of cyclic 3′-nucleotide phosphodiesterase (CNP 2′-3′-cyclic nucleotide 3′-phosphodiesterase), is associated with catatonia. Mice heterozygous according the CNP genotype exhibited axonal degeneration and mild inflammation mediated by microglia and associated with symptoms similar to depression and catatonic disorders [23]. In humans, the rs2070106 polymorphic locus was found in the CNP gene, which is associated with a partial loss of protein function. In this locus, caused by the replacement of the nucleotide adenine (A) by guanine (G), in the group of patients with schizophrenia with the AA genotype, i.e., dominant homozygotes, pronounced signs of catatonia were detected, compared with carriers of the genotype, containing the G allele [24]. However, it should be noted that the linkage strength of the identified mutations with catatonia did not reach the level of statistical significance.

CNVs (copy number variations) are considered as genetic variants with a large effect, which are extended DNA sections, that can differ in duplication or deletion of certain fragments within their structure.

It was shown that the frequency of mutations, in particular, caused by CNVs, in cohorts of patients with catatonia was quite high. For example, in the study by J. Breckpot et al. [25] out of 15 patients with catatonia in combination with psychotic, affective and autistic disorders, 8 subjects were found to have rare CNVs containing duplications and deletions. The cause of catatonia, according to the authors of the work, was microdeletions in 22q13.3 chromosomal region and, possibly, a mutation in the 14q11.2 locus, containing the SUPT16H gene, which encodes chromatin remodeling factors. In confirmation of these results, we can also cite data on the detection of various genetic anomalies in the sample of children with catatonia syndrome, noted in 21.3% of the examined patients. Among them, five CNVs were identified on chromosomes 2, 8, 13, 16, and 22. The sites, associated with catatonia included the 22q13.3 deletion, including the SHANK3 gene, the 16p13 duplication, the 8p23.3 DLGAP2 terminal deletion, and the CLN8, 2q22.1 b, and 13q33.1q34 deletions [26]. In recent years, cases of patients with a mutation represented by a microdeletion in the SHANK3 gene (the gene encoding SH3 and several ankyrin 3 repeat domains) have been reported. In these patients, pronounced manifestations of catatonia were observed, which allowed the authors of the publications to speak of a specific phenotype, caused by the SHANK3 mutation. Unfortunately, the modern genetic method, that is genome-wide analysis, which allows assessing heritability by the total contribution of numerous polymorphic variants, has not yet yielded any significant results in relation to catatonia. This may be due to a fairly wide diagnostic interpretation of catatonic disorders, their clinical heterogeneity and development under different nosological diseases, which requires additional efforts to form relatively homogeneous clinical samples sufficient in size for genome-wide studies.

Another explanation may be due to the fact that, unlike other psychopathological syndromes, catatonia is determined not only by the influence of variants of individual genes with a small effect, but is also associated with significant variations in copies in the genome (CNVs), the effects of which are quite large.

Thus, although genetic studies do not allow identifying specific genes and pathways, that may be involved in the formation of catatonic disorders at the molecular level, they undoubtedly confirm the contribution of genetic factors to their formation. In addition, the genetic features, identified by the authors of the studies, such as CNVs, as well as polymorphisms, not associated with immune function, indicate the possibility of the catatonic disorders formation by molecular mechanisms, not associated with inflammation.

CLINICAL AND BIOLOGICAL PARALLELS IN THE FORMATION OF CATATONIC DISORDERS IN SCHIZOPHRENIA

The presented published materials, as well as the data of our own research, allow us to put forward the following working hypothesis: **the typological**

differentiation of catatonia syndromes is mediated by various molecular mechanisms i.e. nonspecific inflammatory pathogenesis and specific genetic mechanisms, that determine pathways not associated with inflammation.

In other words, on the basis of the proposed hypothesis, the following clinical and biological concept can be formulated: **clinical heterogeneity — differences in the phenotypic manifestations of catatonic disorders in schizophrenia — are determined by nonspecific inflammatory and other processes involved in various ratios, associated with a specific genetic predisposition** (Fig. 1).

The presented scheme (Fig. 1) demonstrates that the phenotype of catatonic disorders and their typological heterogeneity depend on the activity of the inflammatory process. At the same time, genetically determined disorders will manifest themselves in the most pronounced form against the background of fading inflammation (i.e, with the phenomena of parakinetic catatonia).

It can also be assumed, that a change in the ratio of inflammatory and genetic mechanisms (expiring inflammation corresponds the maximum severity of genetically determined disorders) may represent the biological basis for the phenomenon of a repeatedly recurring cycle of the disease, which is often encountered in clinical practice (attack/remission, attack/slowly-progredient course).

In general, a different ratio of inflammatory and genetic mechanisms in the genesis of psychopathological disorders formation determines their psychopathological and immunological variety and it is a wide continuum of these disorders. At one pole of the continuum there are disorders, determined predominantly by inflammatory mechanisms, at the other pole — by predominantly genetic ones.

Comparison of the above immunological and genetic data with the psychopathological characteristics of movement disorders (parakinetic or stereotyped catatonia) presented in the previously cited studies [10–14] creates a basis for the analysis of a more general problem, related to the nature of movement disorders, that appear in the clinical space of schizophrenia and schizophrenia spectrum disorders.

If we compare the identified symptom complexes not from the standpoint of the typological differentiation of catatonia as a single syndromic formation, but at the clinical and pathogenetic level, then it seems possible to distinguish two groups in the clinical space of schizophrenia, which are polar not only in their psychopathological structure,

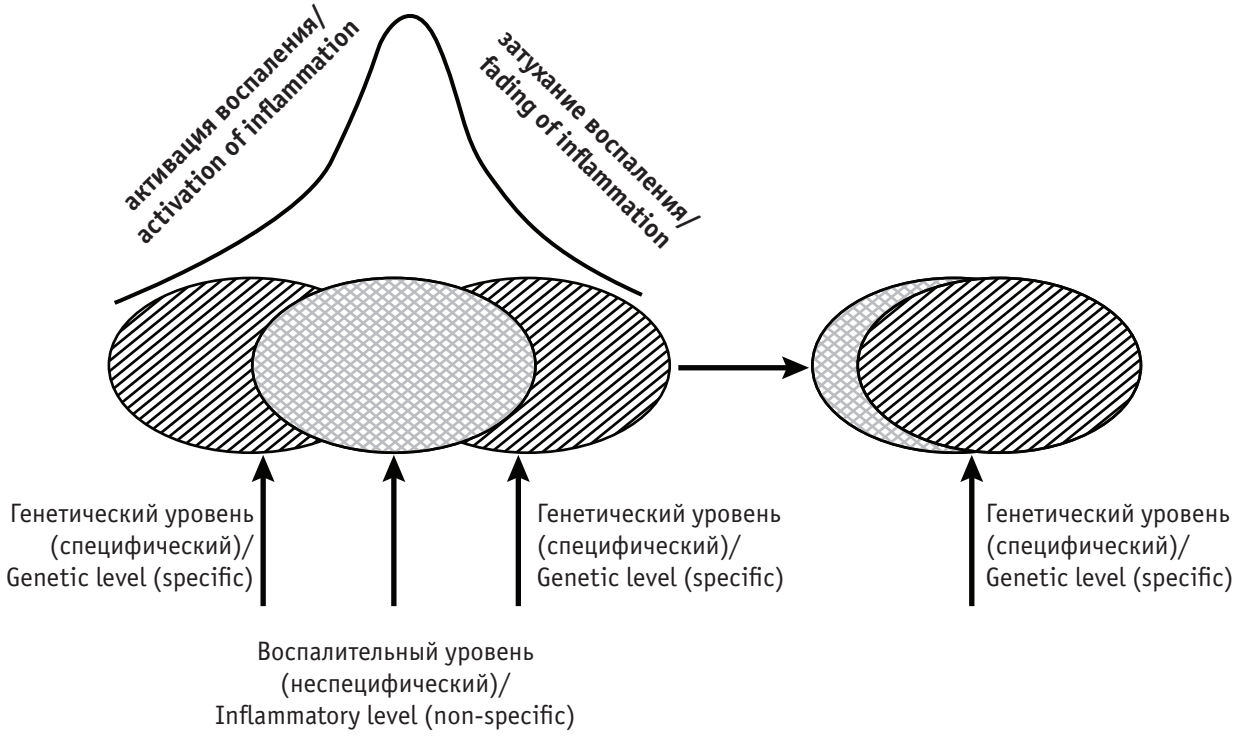

Fig. 1. Ratio of different specific genetic and non-specific inflammation mechanisms in catatonic disorders formation

but also in various pathological processes of their development on the molecular level.

Group 1: these are motor dimensions related to parakinetic catatonia. They represent primary, or basic catatonic disorders (primary positive dimensions according to G. de Clérambault [27], determined mainly by genetically conditioned pathological processes, not associated with inflammatory mechanisms.

In accordance with the data of a psychopathological study, the clinical activity of catatonic dimensional structures of this group is formed according to the mechanism of mental automatism [12]. Accordingly, catatonic symptom complexes act as transformers that aggravate, or replace positive, affective, pathocharacterologic and other disorders, completely determining the clinical picture of the disease.

Group 2: these are affiliated motor dimensions, which are formed mainly on the basis of non-specific inflammation processes (stereotyped catatonia). Catatonic disorders of the second group amplify (and do not deform, unlike the symptom complexes of the first group) manifestations of both negative/cognitive disorders (abulia, passivity, apathy, and emotional flattening, bradyphrenia) and positive (affective) disorders, without modifying their syndromic structure.

The data obtained allow the possibility of extrapolation of the psychopathological construct, developed on the model of catatonia, to a wide range of other positive disorders, such as paranoid, hypochondriac and other formations, that define the psychopathological space of schizophrenia. Clinical and biological study of the problem in this aspect continues in the department of borderline states and laboratories of the MHRC.

CONCLUSION

Based on the analysis of the results of our own clinical and biological studies of catatonic disorders in schizophrenia and schizophrenia spectrum disorders, as well as data from foreign studies in the field of psychogenetics, a new concept of the clinical and biological model of schizophrenia is presented, associated with the participation of a chronic nonspecific inflammatory process and a specific genetic predisposition in the formation of psychopathological dimensions.

The creation of a new clinical and biological concept made it possible to differentiate dimensional structures, which contributed to the identification of the "most pathognomonic positive symptom complexes of schizophrenia" and affiliated dimensions, as well as to hypothetically determine the neurobiological nature of the phenomenon of the disease duplicating cycle.

These new ideas are important for understanding the fundamental basis of the mental illness pathogenesis, as well as for solving a number of practical issues related to the pharmacotherapy of schizophrenia at various stages of the disease, developing new approaches to early diagnosis, clinical and social prognosis.

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