E.G. Kornetova, S.D. Koval', A.N. Kornetov, D.A. Parshukova, S.A. Ivanova, A.V. Semke, S.V. Gusakova, N.A. Bokhan

BRAIN PATHOLOGY IN SCHIZOPHRENIA: ASSOCIATION WITH CLINICAL AND CONSTITUTIONAL FACTORS

DOI 10.25789/YMJ.2019.65.05

ABSTRACT

Aim of study: to find the conjugation between pathological changes of schizophrenia patients brain structures, clinical picture of the disease and its constitutional and morphological features.

Materials and methods. 38 schizophrenia patients with schizophrenia with duration of disorder not less than 1 year and whose condition satisfied the diagnostic criteria of IDC-10 were under study. The study included magnetic resonance imaging, anthropometry, PANSS psychometric evaluation, registering basic clinical signs with hereditary burden, duration of disorder, the main symptoms. The criteria for not including were presenting marked deviations in physical investigation and neurological status, concomitant presence of traumatic brain injuries in anamnesis and other organic disorders, congenital and acquired pathologies of the skeleton system. The investigation participants' mean age was 39.5±11.7 years. Statistics was made using correlation analyses and Mann-Whitney criteria.

Results. The study shows that cysts and dyscirculatory foci are observed more often (14 patients, 36.8%, $p<0.05$) at negative disorders than at a positive domain. In subgroup of patients having prevalence in negative symptoms was found a direct correlation between constitutional-morphological type of patients and the expansion of the big brain hemispheres subarachnoid space ($p<0.05$), and opposite correlation between Tanner indexes and expansion of the cerebellum subarachnoid space ($p<0,05$). It was also found the direct correlation between cysts existence and constitutional-morphological type of patients ($p<0.01$) and the opposite correlation with Rees-Eysenk indexes.

Conclusion. Associations were found between morphological brain pathology, body constitution and clinical manifestations; they display the role of phenotype schizophrenia indications. The study shows that cysts and dyscirculatory points are observed more often at negative disorders than at a positive domain. It may be connected with disontogenesis impact on severity of schizophrenia. There were also found the association between hyperstenic somatotype, increasing of big brain hemispheres subarachnoid areas and gynecomorphy with the expansion of the cerebellum subarachnoid space. The results are important for testing the hypothesis about correlations between brain pathology and clinical and constitutional features of patients with schizophrenia.

Keywords: schizophrenia, negative symptoms, brain morphopathology, MRI, constitutional-morphological type.

Introduction. Current trends in scientific research of complex, multifactor phenomena increasingly consist in attracting interdisciplinary approaches to their study. Schizophrenia is a multifactorial problem and its decision is still intractable using only psychiatric methods. One of possible decisions of this problem could be the attraction of these approaches, which can integrate possibilities to study the morphofunctional unity, taking into account unsuccessful endeavors to find pathognomonic body changes for this disorder as a whole that could be verified by laboratory and instrumental methods, generally acknowledged in medicine.

One of the approaches in study of mental and behavioral disorders is constitutional, namely integrative-anthropological approach [19]. And the most well founded from methodological positions classification, which is used in integrative-anthropological approach, is the three-dimensional classification of constitutional-morphological types.

Besides the somatotype characteristics of patients with schizophrenia, one of good developed clinical anthropometry division is the verification of somatic sex maturation and dysplastic constitution types' [14], which have their own impact on disease process. At the same time, special importance is attached to regional morphological dysplasias, which reflect the dysontogenesis and serve as a factor of unfavorable schizophrenia prognosis [19]. Taking into account a fact that most of morphodysplasias are localized in cranium area [5], the brain morphopathologies investigation, which in fact can find small brain tissue anomaly, are attached the special importance.

As long ago as in the middle of previous century there was a question about one or another small anomaly to certain schizophrenia subtypes. So V.M. Mikhlin [16] found big number of cranium dysplasias using craniography of patients with schizophrenia, and its origin reasons he explained the pre-natal pathology. With making contrast X-ray investigation of 20 sick people and 24 couples of their relatives it was pointed that patients with simple or paranoid forms of the disorder had the size increasing only of third and side ventricles and subarachnoid gaps. Later M. Zapletálek et al. [4] found strong atrophic brain changes at schizophrenia with prevalent negative symptoms, T.K.A. Roberts [21] found brain ventricles extension in patients with schizophrenia with cognitive disturbances, negative symptoms and chronic course of disorder. N.C. Andreasen et al. [2] и T.J. Crow [7] found that the patients with positive and negative symptoms have neuromorphological structural differences, for example, the most frequent brain ventricles expansion have patients with negative symptoms. It appeared to be a neurobiological confirmation of dichotomic schizophrenia hypothesis and contributed the development of the dimensional approach. But in more later comparative studies [9, 23] it was demonstrated that neuromorphological anomalies in different schizophrenia subtypes have no differences. When non-invasive morphological imaging (computed tomography, magnetic resonance imaging) was originated, patients with schizophrenia comparing with healthy volunteers were observed temporal and frontal lobes changes in the form of a decrease in the volume and density of the white matter, as well as in other brain structures, in particular corpus callosum, caudate nucleus, parietal and occipital lobes. During all period of the disease for the patients brain volume decreasing and ventricles volume increasing together with grey matter decreasing is observed, mostly in frontal cortex, thalamus and cerebellum [1, 10]. Most often patients with schizophrenia have widenings of brain ventricular system and subarachnoid spaces, and different disorders of the vascular system: vascular cysts, dilated perivascular spaces, congenital arterial anomalies and impaired venous circulation signs [2, 17]. This vascular anomaly represents both functional and anatomical pathology of cerebral blood circulatory system and mark the current neurodegenerative process and congenital developmental

disorders. So, these and any other studies focus on searching the possible brain schizophrenia substrate or its particular clinical manifestations, but nevertheless there is no research works about the connection of brain pathology and constitutional features of the patients.

The aim of study is to find the conjugation between pathological changes of schizophrenia patients brain structures, clinical picture of the disease and its constitutional and morphological features.

Materials and methods. A morphometric analysis of brain magnetic resonance imaging of 38 patients with schizophrenia who were treated in the Department of Endogenous Disorders Clinic of the Institute of Mental Health was conducted. Europeoid race participants at the age from 18 to 60 years, who have the sickness catamnesis duration at least than 1 year, whose condition at the time of examination satisfied the diagnostic criteria for schizophrenia according to ICD-10 and who were able to give written informed consent, were included in our investigation. Criteria for not including were presence of explicit abnormalities during physical investigation and neurological status, presence of concomitant brain injuries or other organic pathology in anamnesis, congenital or acquired skeleton system injuries. Participants' middle age was 39,5±11,7 years.

According to the principles, accepted in clinical anthropology [19], anthropometric investigation was made according to the V. V. Bunak's methodic in V. P. Chtetsov's modification for adult samples [6] with counting Rees-Eysenk [20], Tanner [3] indexes, for constitutional-morphological types identification (hyposthenic, mesosthenic and hypersthenic) and somatic sex maturation (andromorphy, mesomorphy and gynecomorphy). Neuroimaging was made using MRI which was carried out using a Siemens MAGNETOM Avanto MRI scanner (Germany) 1.5 T in axial and sagittal projections (T2 and T1 weighted spin echo images). The investigation started with standard T2 weighted spin echo images to exclude pathological brain structure changes. A 3D-T1 gradient echo study mode (T1-mpr) was made for anatomical data obtaining with reception a set of slides (slice thickness 1.0 mm). Next sequentially it was received 4 sets of functional data (for each paradigm) in the T2*-gradient echo mode in axial projection (slice thickness 3.0 mm).

Taking into account previously obtained data about association of body build and schizophrenia symptoms leading clinical profile connection [13] and known data about inauspicious course of the disease with dominant negative symptomocomplex [26], the subgroup of patients was divided, who had negative symptoms on the foreground of clinical picture. This subgroup had PANSS verification [12]. These patients had 28,8±6,6 points for negative symptoms severity against 13,9±3,3 points for positive symptoms severity, general score was 84,1±14,9 points. This subgroup consists of 14 patients (36,8%), and they additionally were made a matching of brain MRI with their main constitutional characteristics.

Statistics were made with Statistica 8.0. The Mann-Whitney criteria was used to evaluate the significance differences in quantitative indicators. The Spearman's correlation coefficient was calculated for evaluation of the linear dependence of quantitative data. The obtained data during analysis for the values of the correlation coefficient r=0,5-1,0 with the significance level of differences p<0,05 were accepted as reliable ones.

The study was made according to the protocol, accepted by local ethical committee of the Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Results and discussion. Morphometric analysis of schizophrenia patients' brain MRI showed correlations with some clinical-dynamical indexes: the hereditary burden, disorder duration, leading PANSS symptoms (Table 1).

A connection was found at p<0.05 between the leading domain in the positive/negative symptoms dichotomy framework and the either absence or presence of brain dyscirculatory foci. If the negative disorders prevail in the clinical picture the dyscirculatory foci are observed more often than with positive symptoms. Their appearance has a typical morphological pattern, revealed by magnetic resonance imaging (Fig.).

As the picture shows, the expansion of perivascular spaces and single dyscirculatory foci up to 2-5 mm are visualized in the white matter supratentorially and in the area of the brain legs. Also important is that the patient has brain ventricles extension in their intact form. Their body sizes are 9-10 mm. The third ventricle's size is 12 mm. In the periventricular zones edema is determined. In addition, there was revealedan intermediate sail cyst 23x8 mm. Cerebellum subarachnoid space is extended irregularly. The large brain convexital furrows are deepened a few. The pituitary gland is flattened. Another pronounced brain changes were not found. A bilateral nonexudative sinusitis is a contributing factor.

This picture of patient's brain MRI with negative abnormalities in the foreground illustrates the connection of symptoms with the dyscirculatiory foci presence.

The established dyscirculatory diturbances can be a reflection of the dystrophic and degenerative processes in the brain associated with the disorder. According to neuroimaging data these disorders are recorded more often for schizophrenia patients with severe negative symptoms [2] and combined with liquordynamics and all components of the cerebral circulation disturbances. They can also be attributed to dysontogenesis manifestations, which, as we have already mentioned above, are more often observed in more severe schizophrenia course with the persistent negative symptom complex development. This data confirm previous investigation results, that showed that MRI signs of brain abnormalities in schizophrenia are associated both with the current pathological process and have inborn features [22, 24].

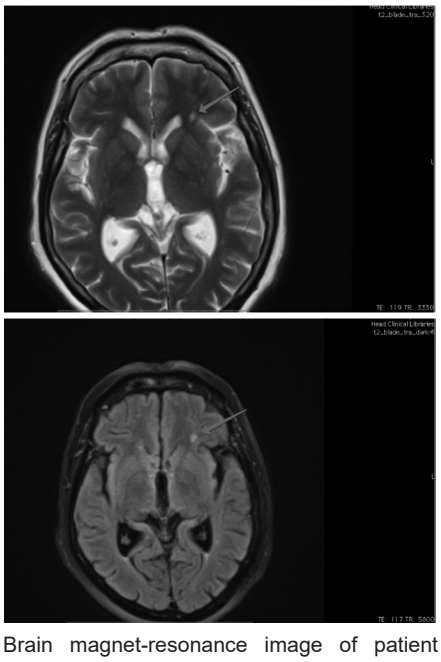
Besides, the brain dyscirculatory dis-

Table 1

Correlation between schizophrenia patient's brain mri with basic clinical-dynamical indexes

MR-parameter	Clinical-dynamical indexes		
	HB	DD	LS
The presence of dyscirculatory foci	–0,0350	0,2691	–0,3549*
Ventricular expansion	0,1178	–0,1994	0,0948
The symmetry of the lateral ventricles	0,1130	–0,2317	0,3013
Left lateral ventricle size (mm)	0,0646	0,1199	–0,0814
Right lateral ventricle size (mm)	0,1303	0,1491	–0,0248
The third lateral ventricle size (mm)	0,0260	0,2941	–0,1716
Periventricular edema	0,2639	0,1997	–0,0781
Subarachnoid space of the big hemispheres	–0,0434	0,1236	–0,0686
Subarachnoid space of the cerebellum	–0,0073	–0,1050	–0,1250
The presence of cysts	–0,0544	0,0712	0,0260

Note: * data with significance p<0,05; HB – hereditary burden; DD – disorder duration; LS – leading symptoms (positive/negative).



Brain magnet-resonance image of patient Ch., female, 55 years old, with schizophrenia negative domain.

turbances in patients with schizophrenia can be caused by long period antipsychotic drugs reception, which reduce the blood pressure, but there is a data [8], that by additional magnet-resonance investigations the vascular pathology features were also discovered by both first-sick patients and patients who had irregular antipsychotic therapy. In previous study [17, 25] in 10% patients with schizophrenia were identified brain development abnormalities, correlated with brain stem, cerebellum and pituitary and with hemodynamic disorders at these brain areas, blood flow decreasing at the dorsolateral cortex of schizophrenia patients with a leading negative symptomocomplex, and other neuromorphological disorders, predominantly the expansion of the brain ventricles with the decreasing of its weight and longitudinal size.

Taking into account previously explicated data a morphometric analyses of schizophrenia patients' brain MRI with negative disorders prevalence according their basic constitutional characteristics was made (Table 2).

Within the subgroup of patients with leading negative symptoms, there were found significant associations between the brain magnetic resonance imaging data and the main constitutional morphophenotype indexes. Particularly, a direct correlation was found between the patients' constitutional-morphological type and the expansion of the big hemispheres subarachnoid space ($p<0,05$) and the reverse correlation between the Tanner index and the expansion of the cerebellum subarachnoid space ($p<0,05$). These found correlations represent that the morphophenotypical shift towards hypersthenia in a negative symptom complex of schizophrenia is associated with an extended subarachnoid space in the cerebral hemispheres. The shift of somatic sexual maturation to gynecomorphy in this domain is associated with the expansion of the cerebellum subarachnoid space. A direct correlation between the presence of cysts with a constitutional-morphological type ($p<0,01$) and the reverse with the Rees-Eysenk index ($p<0,001$) shows that for people of hypersthenic body type with negative symptoms complex the formation of cysts is more characteristically. For the examined patients, they were located in the cortex and the white matter of the left frontal lobe, on the anterior of the left temporal lobe surface, on the convexital of the right temporal lobe surface, in the posterior cranial fossa, intermediate sail, in the cerebellum left hemisphere. At the same time, the localization of cysts, typical of a negative symptom complex, being confirmed at the level of statistical regularities, was not found.

Table 2

Correlation between schizophrenia patients' brain mri with negative disturbances prevalence and their basic constitutional characteristics

MR-parameter	Constitutional characteristics		
	I R-E	KMT	I T
The presence of dyscirculatory foci	–0,2314	0,4341	–0,0927
Ventricular expansion	0,2595	–0,3410	0,1738
The symmetry of the lateral ventricles	–0,0276	–0,0976	0,2375
Left lateral ventricle size (mm)	0,0324	–0,1941	0,1915
Right lateral ventricle size (mm)	0,2556	–0,1920	0,0147
The third lateral ventricle size (mm)	0,2242	–0,0990	–0,2097
Periventricular edema	0,2824	–0,0941	–0,4817
Subarachnoid space of the big hemispheres	–0,4153	0,5630*	0,1093
Subarachnoid space of the cerebellum	0,1636	–0,0296	–0,0690*
The presence of cysts	–0,8354***	0,7233**	0,2450

Note: * data with significance $p<0,05$; ** represents data with significance $p<0,01$; *** data with significance $p<0,001$; R-E I – Rees-Eysenk index; CMT – constitutional-morphological type; T I – Tanner index.

Conclusions. The collected data represent the cysts and dyscirculatory foci are observed more often with negative disturbances than with positive domain. This can be associate with dysontogenesis impact on schizophrenia severity. Also, the correlation was found between hypersthenic somatotype and expanding of the subarachnoid space of big brain hemispheres and gynecomorphy with cerebellum subarachnoid space expanding. The results of the study represent the role of constitution in schizophrenia clinical dynamics, they show its role with brain pathology and can be basis of early prognose for negative disorders. Due to opportune proper treatment it can help to improve care efficacy for this disorder.

This study is limited by using standard MRI for routine clinical practice. Lately, patients with schizophrenia are mainly examine with the functional MRI [18]. In addition, great emphasis is placed for longitudinal neuroimaging studies to identify the dependencies of these brain changes during treatment by various modern antipsychotics [11], and also during the remission formation [15]. However, our results are important for testing the hypothesis about the relationship of cerebral pathology with clinical and constitutional features of patients with schizophrenia.

The study was carried out with the financial support of grants: RSF18-15-00053 "Search of peripheral markers associated with impaired myelination of the brain and pathogenesis of schizophrenia" in part of including of brain MRI examination with the results interpretation, and RSF18-15-00011 "Schizophrenia combined with metabolic syndrome: clinical-constitutional factors and molecular markers" in part of constitutional-morphological examination with the data interpretation.

References

1. Badalyan L.O. Zhurba L.T. Vsevolzhskaya N.M. Rukovodstvo po nevrologii rannego detskogo vozrasta [Early childhood neurology manual]. Kiev: Zdorov'ja [Health], 1980, 528 p.

2. Semke A.V., Fedorenko O.Yu., Lobacheva O.A., Rakhmazova L.D., Kornetova E.G., Smirnova L.P., Mikilev F.F., Shchigoreva Yu.G. Klinicheskie, jepidemiologicheskie i biologicheskie predposylki adaptacii bol'nyh shizofreniej kak osnova personificirovannogo podhoda k antipsihoticheskoj terapii [Clinical, epidemiological and biological preconditions of

adaptation of patients with schizophrenia as a basis for personified approach to antipsychotic therapy]. Sibirskij vestnik psikhiatrii i narkologii [Siberian herald of psychiatry and addiction psychiatry], 2015, №3, pp. 19-25.

3. Kornetov N.A. Koncepcija klinicheskoj antropologii v medicine [Conception of clinical anthropology in medicine]. Byulleten’ sibirskoi meditsiny [Bulletin of Siberian Medicine], 2008, Vol. 7, №1, pp. 7-30.

4. Lebedeva I.S., Kaleda V.G., Barkhatova A.N., Akhadov T.A., Semenova N.A. Markery strukturnogo i funkcional’nogo sostojanija golovnogo mozga pri stanovlenii remissii u bol’nyh junosheskoj shizofreniej [The markers of structural and functional state of brain during remission establishing in the patients with juvenile schizophrenia]. Psihiatrija [Psychiatry], 2013, №2, pp. 26-31.

5. Mikhlin V.M. K voprosu o rentgenologicheskih izmenenijah v kostjah cherepa pri shizofrenii s neblagoprijatnym techeniem [On the issue of radiographic changes in the skull bones in schizophrenia with unfavorable course]. Voprosy kliniki i lechenija psihicheskih zabolevanij [Issues of clinic and treatment of mental illnesses]. Kishinev, 1969. pp. 73-75.

6. Mikhailova I.I., Orlova V.A., Berezovskaya T.P., Shavdaladze N.Z., Minutko V.L. MRT-priznaki anomalij golovnogo mozga u bol’nyh pristupoobraznoj shizofreniej: novye dannye s ispol’zovaniem angiografii [MRI-parameters of brain abnormality in attack-like schizophrenia: new data with angiography using]. Vestnik Rossijskogo nauchnogo centra rentgenoradiologii Minzdrava Rossii [Bulletin of the Russian scientific center for x-ray radiology of the Ministry of health of Russia], 2013, Vol. 1, №13. (cited November 25th, 2018). URL: http://vestnik.rncrr.ru/vestnik/v13/papers/michail_v13.htm

7. Nikityuk B.A., Kornetov N.A. Integrativnaja biomedicinskaja antropologija [Integrative biomedical anthropology]. – Tomsk: Izd-vo Tom. Un-ta [Tomsk: Publisher Tomsk University], 1998, 182 p.

8. Miloserdov E.A., Gubsky L.V., Orlova V.A., Voskresenskaya N.I., Ganisheva T.K., Kaidan T.S. Strukturnye osobennosti mozga u bol’nyh shizofreniej i ih rodstvennikov I stepeni rodstva po dannym morfometricheskogo analiza MP-izobrazhenij mozga [Brain structure peculiarities in patients with schizophrenia and their 1st degree relatives by the data of morphometric analysis of MR-images]. Social’naja i klinicheskaja psihiatrija [Social and clinical psychiatry], 2005, Vol. 15, Is. 1, pp, 5-13.

9. Chtetsov V.P., Izuchenie sostava tela u vzroslogo naselenija: metodicheskie aspekty [The studying of body composition in adults: methodological aspects]. Vestnik Moskovskogo universiteta. Serija 23: Antropologija [Bulletin of Moscow university. Series 23: Anthropology], 2012, №2, pp. 43-52.

10. Shmukler A.B. Problema shizofrenii v sovremennyh issledovanijah: dostizhenija i diskussionnye voprosy [The problem of schizophrenia in contemporary studies: achievements and controversial issues]. Moskva: ID “MEDPRAKTIKA-M” [Moscow.: PH “MEDPRACTICE-M”], 2011, 84 p.

11. Schmitt A., Weber-Fahr W., Jatzko A., Tost H., Henn F.A., Braus D.F. Aktueller überblick über strukturelle magnet-resonanztomographie bei schizophrenie [Current overview of structural magnetic resonance imaging in schizophrenia]. Fortschritte der Neurologie-Psychiatrie [Fortschritte der Neurologie-Psychiatrie], 2001, Vol. 69, №3, pp. 105-115.

12. Andreasen N.C., Olsen S.A., Dennert J.W., Smith M.R. Ventricular enlargement in schizophrenia: relationship to positive and negative symptoms. The American journal of psychiatry, 1982, Vol. 139, №3, pp. 297-302. doi: 10.1176/ajp.139.3.297

13. Brooksbank B.W., MacSweeney D.A., Johnson A.L., Cunningham A.E., Wilson D.A., Coppen A. Androgen excretion and physique in schizophrenia. The British journal of psychiatry: the journal of mental science, 1970, Vol. 117, №539, pp. 413-420. doi: 10.1192/bjp.117.539.413

14. Zapletálek M., Tůma I., Kudrnová K., Hubert J., Cernoch Z. Atrofie mozku u schizophreniku. Klinika a skanograficka studie [Cerebral atrophy in schizophrenics. Clinical and scanning study]. Česká a Slovenská psychiatrie [Czech and Slovak Psychiatry], 1983, №3, pp. 158-163.

15. Crow T.J. The two-syndrome concept: origins and current status. Schizophrenia bulletin, 1985, Vol. 11, №3, pp. 471-486. doi: 10.1093/schbul/11.3.471

16. Crow T.J. A current view of the type II syndrome: age of onset, intellectual impairment, and the meaning of structural changes in the brain. The British journal of psychiatry. Supplement, 1989, Vol. 7, pp. 15-20.

17. Maj M., Galderisi S., Conforti R., Colucci D’Amato A. Gross reversal of brain parieto-occipital asymmetry in a case of DSM-IV simple schizophrenia. Schizophrenia research, 1995, Vol. 14, №3, pp. 265-266.

18. van Haren N.E.M, Cahn W., Hussholff Pol H.E., Kahn R.S. Schizophrenia as a progressive brain disease. European psychiatry: the journal of the Association of European Psychiatrists, 2008, Vol. 23, №4, pp. 245-254. doi: 10.1016/j.eurpsy.2007.10.013

19. Davis R.E., Vanover K.E., Zhou Y., Brašić J.R., Guevara M., Bisuna B., Ye W., Raymont V., Willis W., Kumar A., Gapasin L., Goldwater D.R., Mates S., Wong D.F. ITI-007 demonstrates brain occupancy at serotonin 5-HT□A and dopamine D□ receptors and serotonin transporters using positron emission tomography in healthy volunteers. Psychopharmacology (Berlin), 2015, Vol. 232, №15, pp. 2863-2872. doi: 10.1007/s00213-015-3922-1

20. Kay S.R., Opler L.A., Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophrenia bulletin, 1987, Vol. 13, №2, pp. 261-276. doi: 10.1093/schbul/13.2.261

21. Nielsen M.Ø., Rostrup E., Broberg B.V., Wulff S., Glenthøj B. Negative Symptoms and Reward Disturbances in Schizophrenia Before and After Antipsychotic Monotherapy. Clinical EEG and neuroscience, 2018, Vol. 49, №1, pp. 36-45. doi: 10.1177/1550059417744120

22. Rees W.L., Eysenk H.J. A Factorial Study of Some Morphological and Psychological Aspects of Human Constitution. The British journal of psychiatry: the journal of mental science, 1945, Vol. 91, №382, pp. 8-21. doi: 10.1192/bjp.91.382.8

23. Roberts T.K.A. Brain structure and function in the schizophrenics: A neurobehavioral approach. Psychiatric journal of the University of Ottawa: Revue de psychiatrie de l’Universite d’Ottawa, 1983, Vol. 8, №2, pp. 67-80.

24. Galderisi S., Bucci P., Mucci A., D’Amato A.C., Conforti R., Maj M. ‘Simple schizophrenia’ a controlled MRI and clinical/neuropsychological study. Psychiatry research, 1999, Vol 91, №3, pp. 175-184. doi: 10.1016/s0925-4927(99)00026-8

25. Gur R.E., Turetsky B.I., Cowell P.E., Finkelman C., Maany V., Grossman R.I., Arnold S.E., Bilker W.B., Gur R.C. Temporolimbic volume reductions in schizophrenia. Archives of general psychiatry, 2000, Vol. 57, №8, pp. 769-775. doi: 10.1001/archpsyc.57.8.769

26. Tsapakis E.M., Dimopoulou T., Tarazi F.I. Clinical management of negative symptoms of schizophrenia: An update. Pharmacology & therapeutics, 2015, Vol. 153, pp. 135-147. doi: 10.1016/j.pharmthera.2015.06.008

The authors:

Kornetova E.G. Mental Health Research Institute, Tomsk National Research Medical Center, Russian Acad-

emy of Sciences, 4 Aleutskaya street, 634014, Tomsk, Russian Federation, +73822738775, kornetova@sibmail.com ORCID: 0000-0002-5179-9727

Koval' S.D. Siberian State Medical University, 2 Moskovsky trakt, 634055, Tomsk, Russian Federation, +73822901101-1738, hollowpeople@gmail.com

Kornetov A.N. Siberian State Medical University, 2 Moskovsky trakt, 634055, Tomsk, Russian Federation, +73822901101-1812, kornetov@mail.tomsknet.ru ORCID: 0000-0002-2342-7504

Parshukova D.A. Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, 4 Aleutskaya street, 634014, Tomsk, Russian Federation, +73822723832, susl2008@yandex.ru ORCID: 0000-0003-2760-0252

Ivanova S.A. Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, 4 Aleutskaya street, 634014, Tomsk, Russian Federation, +73822723177, ivanovaniipz@gmail.com ORCID: 0000-0001-7078-323X

Semke A.V. Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, 4 Aleutskaya street, 634014, Tomsk, Russian Federation, +73822724379, asemke@mail.ru 2Siberian State Medical University, 2 Moskovsky trakt, 634055, Tomsk, Russian Federation ORCID: 0000-0002-8698-0251

Gusakova S.V. Siberian State Medical University, 2 Moskovsky trakt, 634055, Tomsk, Russian Federation, +73822901101-1814, kaf.biofizika@ssmu.ru ORCID: 0000-0001-5047-8668

Bokhan N.A. Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, 4 Aleutskaya street, 634014, Tomsk, Russian Federation, +73822724015, mental@tnimc.ru 2Siberian State Medical University, 2 Moskovsky trakt, 634055, Tomsk, Russian Federation. ORCID: 0000-0002-1052-855X

A.A. Toropova, B.A. Muruev, Ya.G. Razuvaeva, I.G. Nikolaeva, A.G. Mondodoev

ANTIOXIDANT ACTIVITY OF A ADAPTOGENIC PLANT REMEDY IN MODEL SYSTEMS *IN VITRO*

DOI 10.25789/YMJ.2019.65.06

ABSTRACT

The antioxidant activity of the dry extract from the complex plant remedy has been studied in model systems *in vitro*. The complex plant remedy includes the following species of medicinal plants: *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench. It has been established that the plant remedy under study inhibits the oxidation of the biological substrate preventing from the destruction of β – carotene (IC_{50}=24.3 μg/ml) and yolk lipoproteids (IC_{50}=65.8 μg/ml) and having membrane stabilizing effect in peroxide (IC_{50}=0.97 μg/ml) and osmotic hemolysis (IC_{50}=0.11μg/ml) of erythrocytes. The complex remedy manifests the radical binding activity for 2,2-diphenyl-1- picrylhydrazyl (DPPH˙) (IC_{50}=61.4μg/ml), superoxide anion-radical (IC_{50}=28.6 μg/ml), nitrogen oxide (IC_{50}=55.3 μg/ml), also for Fe^{2+} (IC_{50}=639.3 μg/ml). The marked antioxidant activity of the tested remedy is due to the complex of biologically active substances (flavonoids, tannins, polyphenolic compounds, phenol carbonic acids, ecdysteroids, etc.) contained in its components.

Keywords: plant remedy, adaptogens, *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench., membrane stabilizing activity, 2.2-diphenyl-1- picrylhydrazyl, superoxide anion-radical, nitrogen oxide.

Introduction. Adaptation providing the body balance control in response to the changes in the external and internal environment is one of the main properties of living beings. The decline in adaptive skills or overstrain of adaptation mechanisms caused by pathogenic affects results in the development of pathological states due to the dysregulation of adaptive mechanisms manifested as so named "civilization diseases". Among dysmetabolic and desadaptative pathologies are: chronic heart insufficiency, cerebral circulatory insufficiency and especially the combination of the heart and brain vessel pathologies, dysfunction of central and peripheral neuroendocrine systems [17; 16]. To increase the resistance of the body to adverse health impact the various groups of medicinal means are used; among them adaptogens having the wide spectrum of pharmacological effects and increasing the resistance of the body to adverse exposure are commonly used. Their capability to regulate the hormone-mediated influence and lipid peroxidation plays a leading role in the mechanism of their effect [15; 19].

In this connection, it seems advisable the use of adaptogens of plant origin which have a systemic action on the body manifesting antioxidant, anti-inflammatory, psychotropic, cardio-protective and other effects due to the synergism of biologically active substances [6; 7; 17; 18; 19].

At the Institute of General and Experimental Biology SB RAS the dry extract has been derived from the complex plant remedy consisting of the aerial part of *Serratula centauroides* (L.), leaves of *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench. Previous experiments have shown that the given complex plant remedy has the marked actoprotective activity increasing physical endurance in rats due to optimization of the energy metabolism [2], as well it manifests anti-stress and anti-depressive effects in chronic stress [9].

The aim of the study is to estimate the antioxidant activity of the adaptogenic plant remedy in model systems *in vitro*.

Material and methods of investigation. The subject of the study was the complex plant remedy in the form of the dry extract consisting of *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench.

The method of the dry extract obtaining involves the extraction of the powdered plant material by 30-70% ethyl alcohol, concentration and drying in the vacuum set [12].

The membrane stabilizing activity of the tested remedy was estimated in the models of peroxide and osmotic hemolysis with the 1% erythrocyte suspension (Er/m). The peroxide hemolysis of erythrocytes was induced by Fenton reagent [22] and osmotic hemolysis – by adding of the distilled water into the incubation medium [4]. The tested plant