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Pharmacogenic and neurologic components of residual condition in schizophrenia

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Aim. To systematize neuroleptic-induced and neurologic components of residual condition in schizophrenia.

Materials and methods. 100 patients of Communal Non-Profit Enterprise "Regional Clinical Institution for the Provision of Psychiatric Care" of Zaporizhzhia Regional Council with diagnosis of recurrent schizophrenia (ICD-10: F20.5) were examined.

Results. The study has found correlations between pharmacotherapy and cerebrovascular pathology with positive and negative symptoms of residual schizophrenia. Noticeable positive correlations were established between specific antipsychotic prescriptions and positive negative schizophrenia symptoms, while only minor correlations with negative symptoms were found.

Analysis of cerebrovascular pathology with positive and negative symptoms showed that most noticeable positive correlations were anterior area stroke with hallucinations.

Overall dominance of negative correlations over positive ones showed possible trend of "forced normalization" caused by cerebrovascular pathology of schizophrenia manifestations in recurrent condition, which was, however, also minor.

Conclusions. The study has found correlations between pharmacotherapy and cerebrovascular pathology with positive and negative symptoms of residual schizophrenia. The concept of "antipsychotic course experience" was introduced.

Ключові слова: залишкова шизофренія, нейролептики, коморбідність, позитивні та негативні симптоми, кореляційний аналіз.

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Фармакогенні та неврологічні компоненти резидуального стану при шизофренії

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Мета роботи – систематизація нейролептичних і неврологічних компонентів у структурі резидуальних станів при шизофренії.

Матеріали та методи. Обстежили 100 пацієнтів КНП «Обласний клінічний заклад із надання психіатричної допомоги» ЗОР із діагнозом резидуальна шизофренія (МКХ-10: F20.5).

Результати. Дослідження показало кореляцію фармакотерапії та цереброваскулярної патології з позитивними і негативними симптомами резидуальної шизофренії. Виявили істотні позитивні кореляції між призначенням конкретних нейролептиків і продуктивними симптомами шизофренії, тільки незначущі кореляції встановили з негативними симптомами.

Аналіз кореляцій цереброваскулярної патології з продуктивними та негативними симптомами шизофренії показав, що найбільш значущі позитивні кореляції – між інсультом передньої частки та галюцинаціями.

Однак загальна перевага негативних кореляцій над позитивними вказує на можливу тенденцію до «примусової нормалізації», спричиненої цереброваскулярною патологією, на прояви шизофренії в рецидивному стані, що також незначуща.

Висновки. У результаті дослідження виявили кореляції фармакотерапії та цереброваскулярної патології з позитивними та негативними симптомами при резидуальній шизофренії. Запровадили поняття про досвід курсу антипсихотичних препаратів.

The concept of residual condition in schizophrenia remains the same since Bleuler's Dementia praecox, which represented natural course of disease, out of advanced therapeutic and diagnostic contexts that came into psychiatric clinic last decades. The most prominent change to the psychiatric condition both on behavioral and neurological levels brought by introduction of antipsychotic therapy that now have conventional status [4]. Antipsychotic era is characterized by domination of pure pharmacotherapy over all other treatment options [7,4].

Besides side effects and retarded negative impact of antipsychotic therapy as psychomotor symptoms, there are signs of schizophrenia negative symptoms amplification which conceptualized in "Neuroleptic-induced deficit syndrome" (NIDS) [6,8,9,11].

Historical overview shows relation of organic brain damage and psychotic symptoms of schizophrenia, that was exploited in pre-neuroleptic era in the key of psychosurgery. Psychiatric comorbidity in cases of schizophrenia and pathology that causes organic brain impairment (epilepsy or alcoholism) reveals the presence of so-called "forced normalization". The nature of this concept is in milder schizophrenia and relatively mild schizophrenia course in cases with organic comorbidity. However, these findings are non-systematic [1,8,9].

On the other hand, major studies are aimed at specific for schizophrenia risk factors of organic brain damage, as antipsychotic systematic use, lack of interest in preventive medicine among patients, lifestyle associated and behavioral risks [10].

Some schizophrenia symptoms are complicated to differentiate with organic equivalents that are common in frontal and temporal lobes impairment [2,3,5,12].

The organic comorbidity combined with NIDS impact on psychiatric condition creates a dramatic gap in understanding of contemporary concept of residual condition in schizophrenia.

Aim

To systematize neuroleptic-induced and neurologic components of residual condition in schizophrenia.

Materials and methods

A study was conducted including 100 patients with diagnosis of recurrent schizophrenia (ICD-10: F20.5) at Communal Non-Profit Enterprise "Regional Clinical Institution for the Provision of Psychiatric Care" of Zaporizhzhia Regional Council in the period of 2010–2020. Gender distribution was 71 (71 %) male and 29 (29 %) female patients. The mean age was 55.0 ± 13.1 years, the mean disease duration was 31.2 ± 13.1 years, the mean age of clinical manifestation was 24.1 ± 8.9 years.

Basic characteristics of the disease course due to known medical history in the study contingent were: simple form diagnosis (ICD-10: F20.6) prior to recurrent (3 %); paranoid form diagnosis (ICD-10: F20.0) prior to recurrent (92 %); catatonic form diagnosis (ICD-10: F20.2) prior to recurrent (2 %); hebephrenic form (ICD-10: F20.1) prior to recurrent (1 %); constantly progressive dynamic type (57 %); paroxysmal-progressive dynamic type (35 %); paroxysmal dynamic type (8 %); full ("type A") remissions (1 %); partial ("type B") remissions (9 %); minor ("type C") remissions (58 %); absence of remissions (32 %); 2 or more annual hospitalization stereotype (24 %); 1 annual hospitalization stereotype (34 %) less than 1 annual hospitalization stereotype (40 %).

Neurological anamnesis showed distribution of cerebrovascular (CV) pathology: no signs of any CV pathology were found in 24 % of patients. Signs of CV catastrophes were found in 27 % of patients – ischemic stroke in the anterior meningeal area (6 %), ischemic stroke in the medial meningeal area (9 %), ischemic stroke in the posterior meningeal area (5 %), ischemic stroke in the vertebrobasilar area (5 %), recurrent ischemic stroke of any localization (4 %). Chronic CV diseases were found in 76 % of patients – cerebral atherosclerosis (38 %), stage I arterial hypertension (45 %), stage II (21 %), stage III (6 %). CV persistent conditions were found in 39 % of patients – posttraumatic brain injury (18 %), minor diffuse brain impairment (36 %)

The concept of "Antipsychotic course experience" (ACE) is used to evaluate specific antipsychotic treatment in single hospitalization. Most common prescribed antipsychotics were chlorpromazine (CHZ, 48.3 %), haloperidol (HPD, 66.7 %), trifluoperazine (TFP, 51.7 %), clozapine (CZP, 60.0 %), chlorprothixene (CPX, 73.3 %), risperidone (RPD, 51.7 %), zuclopenthixol (ZPX, 41.7 %) and their various combinations.

The main methods of the examination were clinical data evaluation using criteria and diagnostic categories of the "Positive and negative syndrome scale" and statistical analysis: the normality of the distribution was assessed using the Shapiro–Wilk test. Nonparametric methods of statistical analysis were used. The significance of differences in qualitative characteristics was assessed using Pearson's criterion χ^2; in small study groups, Fisher's exact method was also used to calculate the significance of differences in qualitative characteristics. Correlations between indica-

Table 1. Correlates of antipsychotic prescriptions

ACE	CPZ	HPD	TFP	CZP	CPX	RPD
Chlorpromazine (CPZ)	1					
Haloperidol (HPD)	0.52	1				
Trifluoperazine (TFP)	-0.01	-0.29	1			
Clozapine (CZP)	0.15	0.12	0.02	1		
Chlorprothixene (CPX)	-0.29	-0.08	0.03	-0.61	1	
Risperidone (RPD)	0.05	0.25	-0.10	0.10	-0.05	1
Zuclopenthixol (ZPX)	0.10	-0.11	0.15	0.08	0.07	-0.05

Table 2. Contingent PSS rating

Tag	Symptom	M	m
P1	Delusions	2.0	0.5
P2	Conceptual disorganization	4.3	0.3
P3	Hallucinations	2.0	0.5
P4	Excitement	2.4	0.4
P5	Grandiosity	1.2	0.2
P6	Suspiciousness/persecution	2.0	0.4
P7	Hostility	2.0	0.3

Table 3. Contingent NSS rating

Tag	Symptom	M	m
N1	Blunted affect	4.3	0.2
N2	Emotional withdrawal	3.9	0.4
N3	Poor rapport	3.8	0.3
N4	Passive/apathetic social withdrawal	3.6	0.3
N5	Difficulty in abstract thinking	2.9	0.3
N6	Lack of spontaneity and flow of conversation	3.1	0.3
N7	Stereotype thinking	2.4	0.4

Table 4. PSS and ACE correlations

PSS	CPZ	HPD	TFP	CZP	CPX	RPD	ZPX
Delusions	0.04	0.10	-0.02	-0.13	-0.05	0.37	0.01
Conceptual disorganization	0.10	0.09	-0.02	0.26	-0.18	-0.04	0.09
Hallucinations	0.16	0.16	0.18	-0.19	0.11	-0.07	0.05
Excitement	0.23	0.07	-0.06	0.08	-0.07	0.17	0.34
Grandiosity	0.02	0.11	-0.03	0.02	-0.01	0.35	-0.24
Suspiciousness/persecution	0.13	-0.03	-0.01	-0.21	-0.05	-0.02	0.25
Hostility	0.11	-0.23	0.04	-0.07	0.04	-0.01	0.40

Table 5. NSS and ACE correlations

NSS	CPZ	HPD	TFP	CZP	CPX	RPD	ZPX
Blunted affect	0.07	0.02	0.14	0.17	-0.12	0.03	-0.01
Emotional withdrawal	0.05	0.02	0.03	0.07	-0.01	-0.15	-0.03
Poor rapport	-0.07	0.14	-0.08	0.12	-0.05	0.03	0.02
Passive social withdrawal	-0.12	0.03	0.02	0.16	-0.17	-0.01	-0.25
Abstract thinking	-0.21	-0.04	0.04	-0.10	-0.02	-0.18	-0.14
Lack of conversation flow	-0.06	0.02	-0.02	-0.05	-0.11	-0.17	-0.02
Stereotyped thinking	0.01	-0.04	0.08	-0.01	0.09	-0.10	0.08

Table 6. PSS ratings and OBI inducing factor correlations

CV pathology	P1	P2	P3	P4	P5	P6	P7
Anterior area stroke	0.01	-0.15	0.18	-0.02	-0.02	0.01	0.06
Medial area stroke	-0.10	0.09	0.07	0.01	-0.11	-0.08	0.05
Posterior area stroke	0.08	-0.10	0.10	0.03	0.05	-0.03	-0.01
Vertebrobasilar stroke	0.11	0.08	0.03	0.10	-0.08	0.07	0.07
Recurrent stroke	0.01	0.10	0.01	0.09	-0.07	0.08	0.03
Cerebral atherosclerosis	-0.02	-0.09	-0.12	-0.04	0.06	0.12	0.05
Arterial hypertension 1	0.11	-0.03	-0.09	-0.01	0.05	-0.07	-0.11
Arterial hypertension 2	0.27	-0.06	0.09	0.08	0.12	0.10	0.06
Arterial hypertension 3	0.06	0.07	-0.04	0.18	0.26	0.05	0.11
Traumatic brain injury	-0.02	0.02	-0.05	0.01	0.01	-0.01	-0.01
Minor brain impairments	0.08	-0.10	-0.13	-0.03	0.14	0.05	-0.04

Table 7. NSS ratings and OBI inducing factor correlations

CV pathology	N1	N2	N3	N4	N5	N6	N7
Anterior area stroke	-0.07	-0.07	-0.22	-0.04	-0.02	-0.07	-0.12
Medial area stroke	0.01	0.10	0.02	0.09	-0.11	0.01	0.01
Posterior area stroke	-0.04	-0.11	-0.06	0.11	-0.03	-0.16	-0.15
Vertebrobasilar stroke	-0.10	0.06	-0.15	-0.08	-0.11	-0.07	-0.00
Recurrent stroke	-0.03	0.07	0.01	-0.01	0.01	0.15	-0.07
Cerebral atherosclerosis	0.07	0.10	0.12	0.04	-0.08	0.05	0.01
Arterial hypertension 1	0.05	0.06	0.05	-0.11	-0.07	-0.04	0.03
Arterial hypertension 2	-0.01	-0.12	-0.08	-0.01	-0.09	-0.10	-0.11
Arterial hypertension 3	-0.07	0.01	-0.03	-0.13	-0.06	0.03	0.06
Traumatic brain injury	-0.10	-0.35	-0.05	-0.10	-0.00	-0.16	0.04
Minor brain impairments	0.08	0.06	0.11	-0.01	-0.07	0.06	0.16

tors were calculated using Spearman's rank correlation coefficient (r). Correlation ratios were classified according to the Chaddock scale. Statistical processing of the study results was performed on a PC using the program Statistica 13.0 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results

The retrospective section of the study was aimed at analysis of specific antipsychotic combination (ACE) structure among the study contingent (*Table 1*).

Moderate positive correlations were found for CPZ and HPD prescription rates (r = 0.52) reflecting a traditional intensive therapy model for hallucinatory-paranoid syndrome where CPZ used for psychomotor excitement leveling, and HPD for hallucination reduction. Weak positive correlations were found between RPD and HPD prescription rates (r = 0.25) which reflected a trend of RPD usage as a CPZ atypical substitute. Noticeable negative correlations were found for CZP and CPX (r = -0.61), and CPZ and CPX (r = -0.29) that was caused by avoidance of dangerous α_1 antagonism effects; CPZ and TFP (r = -0.29), and TFP and HPD (r = -0.29) negative correlations resulting from a possible sedative effect amplification.

Prospective section of the study was aimed at positive and negative schizophrenia symptom evaluation among the study contingent (*Table 2, 3*).

Among positive symptoms rating among the study contingent, only conceptual disorganization (4.3 ± 0.3) reached a moderate level of intensity, that represented a specific recurrent condition of patients with pronounced reduction of major part of positive schizophrenia manifestations.

The next section of the study was aimed at finding correlative relations between PPS (*Table 4*) and NSS (*Table 5*) ratings with ACE.

Noticeable positive correlations were established between RPD ACE and delusions (r = 0.37) and grandiosity (r = 0.35); ZPX ACE and excitement (r = 0.34) and hostility (r = 0.40). However, there was no consistent data to find direction of such relations, so it represented both therapeutic tactics focused on dominant symptoms and parameters of remaining positive symptoms in a residual state.

There were no noticeable correlations between ACE and NSS. However, week positive ones were found for HPD and CZP; week negative ones – for CPX, RPD and ZPX that showed possible minor impact of specific antipsychotics on negative symptoms.

The next section of the study was focused on an analysis of CV pathology correlations with PSS (*Table 6*) and NSS (*Table 7*).

Only weak correlations were found between PSS and CV pathology. Most noticeable positive correlations were between the anterior area stroke and hallucinations (r = 0.18); stage II arterial hypertension and delusions (r = 0.27); stage III arterial hypertension and grandiosity (r = 0.26) and excitement (r = 0.18). Negative correlations were overall minor.

For NSS ratings, we have found mostly weak correlations. The only moderate negative correlation was found for traumatic brain injury with conceptual disorganization (r = -0.35). Other noticeable correlation was revealed between anterior area stroke and poor rapport (r = -0.22). However, overall dominance of negative correlations over positive ones showed possible trend of "forced normalization" caused by CV pathology influence on schizophrenia manifestations in recurrent condition, which was however also minor.

Conclusions

1. The study has found correlations of pharmacotherapy and cerebrovascular pathology with positive and negative symptoms in residual schizophrenia in the period 2010–2020. The concept of "antipsychotic course experience has been introduced.

2. Noticeable positive correlations were established between risperidone prescription and delusions (r = 0.32) and grandiosity (r = 0.32); zuclopenthixol prescription and excitement (r = 0.30) and hostility (r = 0.35). However, there was no consistent data to find direction of such relations, so it represented both therapeutic tactics focused on the dominant symptoms and parameters of remaining positive symptoms in residual state. Week negative correlations of chlorprothixene, risperidone and zuclopenthixol with negative schizophrenia symptoms have been found that could show possible minor impact of these specific antipsychotics on negative schizophrenia symptoms.

3. Analysis of cerebrovascular pathology with positive and negative symptoms has shown that most noticeable positive correlations were revealed between anterior area stroke and hallucinations; stage II arterial hypertension and delusions; stage III arterial hypertension and grandiosity and excitement. Negative correlations of cerebrovascular pathology with positive symptoms were overall minor. For

negative symptoms, all correlations have been found to be weak except one was moderately negative (traumatic brain injury and conceptual disorganization of thinking). Other noticeable correlations have been found between anterior area stroke and poor rapport. However, overall dominance of negative correlations over positive ones showed possible trend of "forced normalization" caused by cerebrovascular pathology influence on schizophrenia manifestations in recurrent condition, which was however also minor.

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