Personalized Psychiatry and Neurology

Case Report

Hematological Predictors of Antipsychotic-Induced Metabolic Syndrome in a Female Patient with Schizophrenia: Case Report

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Abstract: Schizophrenia is a chronic mental disorder. It is treated with antipsychotics, which have a high risk of adverse reactions. One of these adverse reactions is metabolic syndrome, which increases the risk of cardiovascular diseases and the mortality rate of patients with schizophrenia. Various studies have shown an association between hematological parameters and metabolic syndrome. In this regard, the use of hematological predictors as a diagnostic tool can help identify risks and timely correct antipsychotic therapy for preventing metabolic syndrome. One of the most promising predictors are hematological inflammation coefficients obtained on the basis of a clinical blood test. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and the index of systemic immune inflammation (SII), are inexpensive, easy-to-detect markers of systemic inflammation. This case report of a 48-year-old female patient with paranoid schizophrenia, hematological inflammation coefficients were increased during antipsychotic therapy compared to the baseline. At the start of clozapine therapy, the highest levels of systemic inflammatory markers were recorded, after which the patient developed metabolic syndrome. In this case, stopping clozapine therapy when the level of hematological inflammatory coefficients increases would prevent the development of metabolic syndrome in the patient. Markers of systemic inflammation can help doctors diagnose metabolic syndrome early. This may reduce rates of cardiovascular disease and type 2 diabetes and thus reduce mortality in patients with schizophrenia. This case report demonstrates that wider implementation of hematological predictors of metabolic syndrome into real clinical practice could help significantly improve the safety of antipsychotic therapy.

Keywords: schizophrenia; metabolic syndrome; antipsychotic; clozapine; hematological inflammation coefficients; adverse reaction

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1. Introduction

Schizophrenia is a severe, chronic mental illness that affects approximately 1% of the population [1]. However, the etiology, pathogenesis and optimal therapy of this disease continue to be studied. In recent years, the role of inflammation in the occurrence of schizophrenia and the development of adverse reactions during its treatment has been

actively studied. It is widely believed that schizophrenia is associated with chronic systemic inflammation [2]. Inflammation is a complex pathophysiological process based on multiple biological pathways and is highly correlated with oxidative stress [3]. It was previously believed that the central nervous system is well protected from peripheral inflammatory agents by the blood-brain barrier. However, this is not true because inflammation increases the permeability of the blood-brain barrier and increases the likelihood of leukocytes entering the brain [4].

It is known that the life expectancy of patients with schizophrenia is significantly lower than in the general population. These patients are more likely to have cardiovascular, respiratory, and metabolic disorders [5]. Cardiovascular disease is the most common cause of death in these patients [5]. Antipsychotic drugs are indispensable for the treatment of schizophrenia; they have been proven to reduce the frequency of relapses and have been used for many years [6]. However, despite the emergence of new antipsychotics, the problem of adverse reactions when taking them remains relevant. The accumulated experience in predicting adverse reactions suggests that many of them can be prevented or their frequency reduced [7].

One of the serious antipsychotic-induced adverse drug reactions (ADRs) is metabolic syndrome. The American Heart Association and the National Heart, Lung, and Blood Institute define metabolic syndrome as a group of correlated metabolic risk factors that predispose an individual to the development of atherosclerotic cardiovascular disease [8]. The International Diabetes Federation defines metabolic syndrome as the presence of central obesity (defined as waist circumference or body mass index > 30 kg/m2) and 2 of the following criteria: systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg, triglycerides ≥ 1.7 mmol/L, HDL < 1.03 mmol/L (men) or < 1.29 mmol/L (women), fasting blood sugar ≥ 5.6 mmol/L or diagnosed type 2 diabetes [8].

Risk factors such as diabetes, hypertension and hyperlipidemia play a significant role in the development of cardiovascular diseases in people with metabolic syndrome. These factors contribute to the progression of atherosclerosis and increase the risk of stroke, coronary artery disease, peripheral artery disease and renal artery stenosis. Understanding the relationship between inflammatory markers in the blood and metabolic syndrome can help identify individuals at high risk of developing it and determine preventive measures. Various studies have shown an association between hematological parameters and metabolic syndrome [9]. Prevention of metabolic syndrome requires timely adjustment of antipsychotic therapy.

Using hematological predictors as a diagnostic tool can help identify risks and take preventive measures against them. It is known that markers of systemic inflammation obtained from clinical blood tests reflect the level of oxidative stress in schizophrenia [3]. One of the most promising predictors are hematological inflammation coefficients obtained on the basis of a clinical blood test. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and the index of systemic immune inflammation (SII), calculated as the ratio of the product of the platelet count by the number of neutrophils to the number of lymphocytes, are inexpensive, easy-to-detect and count markers of

systemic inflammation [10; 11]. Studies have confirmed that these indicators correlate with cardiovascular disease and mortality [12]. Moreover, some of these biomarkers differ by gender [13].

The purpose of this case report is to present the possibility of preventing metabolic syndrome during antipsychotic therapy using hematological inflammation coefficients.

2. Materials and Methods

2.1. Inclusion and Exclusion criteria

The following inclusion criteria were used in selecting patient: signed voluntary informed consent; age over 18 years; established diagnosis F20.00 (schizophrenia); taking antipsychotics. The following exclusion criteria were used in selecting patient: not signed voluntary informed consent; age less than 18 years; diagnosis other than F20.00 (schizophrenia); not taking antipsychotics; the presence of acute inflammatory diseases; the presence of decompensated chronic somatic diseases.

The patient was observed at the V. M. Bekhterev National Medical Research Center for Psychiatry and Neurology, St.-Petersburg, Russia.

2.2. Procedure

Blood was taken from a peripheral vein in a volume of 5 ml every two weeks throughout hospitalization. Clinical analysis of the patient's blood sample was carried out in a certified laboratory using an automatic hematology analyzer XP-300 (Japan).

2.3 Ethical Considerations

The study was conducted in accordance with the standards of clinical practice and the principles of the Declaration of Helsinki. Clinical testing was carried out within the framework of a state order. The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical study.

3. Case Report

Patient K., 48 years old.

The patient's early development without features. She has secondary specialized education. She worked in her specialty for a short time, then she worked as a cleaner, but has not worked for several years yet. She is divorced and now lives with his daughter, communicates only with her. The patient's daughter is seen by a psychiatrist with a diagnosis of paranoid schizophrenia.

The time of onset of the disorder cannot be reliably determined. It is known that over the past 20 years the patient has been a gradual social decline, with a limitation of the social circle to one person, a decrease in working ability, and social maladaptation. Since the spring of 2019, she has been a feeling that what is happening is being rigged. It

seemed that the people around her knew everything about her. The patient's daughter insisted on visiting a psychiatrist, after which the patient underwent inpatient treatment for the first time. Upon admission to the hospital, a state of severe psychomotor agitation developed, and she suspected the doctors of wanting to "harm" her and her daughter. She screamed, asked to "let her go," "not to close her," and fell to the floor. She refused to call her daughter for delusional reasons. During therapy with haloperidol up to 10 mg/day, delusional ideas were reduced and she became calm. Subsequently, she was repeatedly hospitalized in a psychiatric hospital with the resumption of previous symptoms due to the withdrawal of maintenance therapy.

Recent hospitalizations were associated with severe anxiety, suspicion, stated that she was surrounded by robots, believed that all people, including herself, were "robots", reported the presence of "voices" in her head with imperative content, including those demanding to hit surrounding people. Resists the orders of the "voices", but not always successfully.

Mental status on admission: Correctly oriented. Anxious, unstable mood, tense, suspicious. During the conversation, she looks around. Emotional reactions are smoothed out, facial expressions are poor, the voice is poorly modulated. Answers questions briefly, monosyllabically, selectively, not always in terms of the questions asked. Reports that he hears extraneous "voices" in his head with unpleasant content. She expresses delusional ideas about staging, believes that people do not exist, everyone around is robots and monsters, including her. She cannot explain his opinion or provide evidence for this. Cannot be persuaded. Plans for the future are amorphous.

Dynamics of the condition: due to poor tolerability of antipsychotic therapy, therapy was selected for a long time. The intensification of therapy was poorly tolerated. During therapy with typical antipsychotics and most atypical ones in high doses, symptoms of neurolepsy and collaptoid states quickly develop with long periods of restoration of a satisfactory somatic state. A significant increase in body weight and the formation of metabolic syndrome were also recorded (Table 1).

Table 1. Results of laboratory and anthropometric examination when selecting antipsychotic therapy

Antipsychotic	**Dose (mg/day)**	**Body mass index (kg/m^2)**	**Blood pressure (mmHg)**	**Fasting glucose (mmol/l)**	**NLR**	**MLR**	**SII**
Before therapy		28.8	110/70	4.4	1.5	2.9	492.0
Haloperidol	6	3.4	120/80	4.5	2.1	3,2	594.8
Paliperidone	6	33.2	120/75	4.4	2.7	3.0	480.6
Olanzapine	10	34.2	120/80	4.9	1.8	3.4	479.8
Olanzapine	20	36.9	130/80	4.8	2.5	5.3	579.2
Amisulpride	800	35.4	120/75	4.9	2.5	2.8	577.0
Clozapine	100	37.0	140/90	5.4	3.3	3.6	948.8

Clozapine	200	37.9	160/100	5.8	2.8	3.2	764.2
Clozapine	300	39.6	150/90	5,8	2.6	2.3	740.5
Aripiprazole	30	32.5	120/80	5.2	2.1	2.5	537.9

Note: NLR - neutrophil-to-lymphocyte ratio; MLR - monocyte-to-lymphocyte ratio; SII - the index of systemic immune inflammation

The most optimal therapy in terms of effectiveness and safety for this patient was therapy with aripiprazole at a maximum dose of 30 mg/day. Thanks to her, it was possible to achieve deactualization of delusions and hallucinations, the patient became orderly in her behavior and statements. Therefore, she was discharged home in satisfactory condition.

4. Discussion

In the presented clinical case of a female patient with schizophrenia, hematological inflammatory coefficients were increased during antipsychotic therapy compared to the baseline throughout the hospitalization. This is consistent with Özdin et al. (2019), according to which markers of systemic inflammation show higher levels in schizophrenia during relapse than during remission [14]. However, this fact is not entirely consistent with the study by Zhou et al. (2020), according to which NLR increases with the severity of psychopathology in schizophrenia and decreases with the prescription of antipsychotics [15]. An explanation for this discrepancy may be that antipsychotics themselves can cause inflammatory damage if their doses are too high for the person being treated [16]. Frota et al. (2023) suggest that because NLR is positively correlated with antipsychotic dose calculated by chlorpromazine equivalent, it appears that female patients are more sensitive than men to the effects of these drugs, thus a positive correlation between antipsychotic dose and NLR suggests an increased burden of side effects in women [2]. In other words, women, on average, have a more favorable course of schizophrenia than men, at least during their reproductive years, perhaps because some estrogen receptors (such as G protein-coupled estrogen receptor 1) mediate anti-inflammatory effects [2]. Therefore, it is advisable to treat women with lower doses of antipsychotics. Many women receive unnecessarily high doses because existing dosing studies have been conducted primarily in men [17]. Seeman et al. (2020) comes to the same conclusion [18]. The authors show that the clinical effects of antipsychotics differ depending on the patient's gender, and also note that cardiovascular mortality, to which men are generally more susceptible than women, increases disproportionately in women when treated with antipsychotics [19]. According to them, estrogen has a direct antipsychotic effect on brain receptors and modulates the metabolism of some antipsychotics [19]. Due, at least in part, to these mechanisms, women with schizophrenia of childbearing age require lower doses of antipsychotics than men [18].

The formation of metabolic syndrome in this clinical case occurred during clozapine therapy. Noteworthy are the highest rates of NLS and SII for the entire period of hospitalization at the very beginning of clozapine therapy at a still low dose of 100 mg/day. Thus,

stopping clozapine therapy when the level of hematological inflammatory coefficients increases would prevent the patient from developing metabolic syndrome. According to a study by Cordova et al. (2023) clozapine users had significantly higher neutrophil counts ($5.03 \pm 2.07 * 10^9$/L) compared to clozapine non-users ($3.48 \pm 1.27 * 10^9$/L), $p = 0.031$ [4]. Although no significant differences were observed in other parameters, clozapine users tended to have higher levels of systemic inflammatory markers, with the exception of monocytes and MLR, which were lower in clozapine users [4]. These results are consistent with experimental studies in animal models: an increase in neutrophils and a decrease in lymphocytes was observed several hours after a single dose of clozapine [19]. Although this seems counterintuitive, since one of the serious adverse reactions of clozapine is leukopenia and agranulocytosis, which occurs in 1–2% of patients, some studies have already linked clozapine to inflammatory effects leading to myocarditis and fever [21 – 23]. Also in the study by Cordova et al. (2023) assessed the correlation between the level of inflammatory markers and the daily dose of clozapine, but did not find statistical significance [4]. Additionally, no correlation was found between inflammatory markers and symptom severity [4].

5. Conclusion

In the presented case report, a patient with schizophrenia developed metabolic syndrome while on clozapine therapy. In this case, stopping clozapine therapy when the level of hematological inflammatory coefficients increases would prevent the development of metabolic syndrome in the patient. Markers of systemic inflammation, which are included in a routine complete blood count, can help physicians in the early diagnosis of metabolic syndrome when combined with existing diagnostic criteria. This could help stem the tide of the rapidly rising burden of metabolic disorders that subsequently lead to much more severe diseases, including cardiovascular disease and type 2 diabetes. However, at present, the calculation of these indicators is not part of the standard of clinical practice and is not included in the routine method of examining patients. This case report demonstrates that wider implementation of hematological predictors of metabolic syndrome into real-world clinical practice could help significantly improve the safety of antipsychotic therapy.

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