PPN

Personalized Psychiatry and Neurology

Case Report

Clinical Case of a 36-year-old Patient with Paranoid Schizophrenia and Drug-Induced QT Prolongation

Nikita M. Zhuravlev[1]*, Andrey P. Otmachov[2], Anna E. Bartasinskaya[2]

[1] V.M. Bekhterev National Research Center for Psychiatry and Neurology, 192019 Saint Petersburg, Russia;

[2] Hospital named after P.P. Kashchenko, 190005 Saint Petersburg, Russia

* Correspondence: nikita.m.zhuravlev@yandex.ru (N.M.Z.); Tel.: +7(812)670-02-20.

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Abstract: Heart rhythm and conduction disorders are a serious problem in chronic psychopharmacotherapy of schizophrenia. One potentially fatal antipsychotic-induced adverse reaction is drug-induced long QT syndrome, which is a phenomenon of prolongation of cardiac repolarization and leads to an increased risk of ventricular tachycardia, known as Torsades de pointes, in the presence of an administered drug [1]. The clinical diagnosis of this adverse drug reaction is difficult, however, electrocardiography and Holter ECG monitoring are the gold standard for the functional diagnosis of long QT syndrome, although they do not give the psychiatrist an answer about the possible correction of mono- or polytherapy for schizophrenia in a particular patient. Pharmacogenetic testing is an integral part of the personalized strategy of psychopharmacotherapy in modern psychiatry. Slowing the efflux of antipsychotics through the histohematic barriers and the membrane of neurons and cardiomyocytes, along with slowing down the metabolism of antipsychotics in the liver with the participation of cytochrome P450 enzymes, can significantly increase the risk of antipsychotics induced long QT syndrome and sudden death syndrome. The purpose of this clinical case is to update the existing problem of pharmacogenetic testing in real psychiatric practice and demonstrate possible ways to solve the problem of antipsychotic-induced long QT syndrome in a young man with paranoid schizophrenia.

Keywords: *schizophrenia; therapeutic resistance; adverse reaction; antipsychotics; pharmacogenetic testing; long QT syndrome*

Introduction

Schizophrenia (Sch) is one of the serious and socially significant mental disorders, the prevalence of which reaches millions of cases in the world. For the treatment of Sch, antipsychotics (APs) are the drugs of first choice. [2].

Despite the generation of new APs, the problem of AP-induced adverse drug reactions (ADRs) from various organs and systems has not been resolved. ADRs on the part of the cardiovascular system is considered life-threatening, since it increases the risk of fatal outcomes. One of these ADRs is AP-induced long QT syndrome (LQTS), which is a prolongation of the QT interval against the background of antipsychotics taken [1].

LQTS remains an urgent problem of psychopharmacotherapy, and the accumulated experience in its targeted prevention suggests that most of them can be prevented or their consequences can be significantly reduced, including sudden death syndrome (SDS).

Along with the detection of mutations in causal genes responsible for familial and sporadic monogenic forms of LQTS, and single nucleotide variants (SNVs) of candidate genes responsible for multifactorial forms of LQTS [3], the study of the mechanisms of development of AP-induced LQTS is based on changes in their metabolism and AP transport, which, in turn, depend on other risk factors for the development of ADRs:

- modifiable factors (choice of APs, its dose, dosing regimen, consideration of comorbid conditions, etc.);
- modifiable factors (gender, age of patients, genetic predisposition).

Objective

The purpose of this clinical case is to update the existing problem of pharmacogenetic testing in real psychiatric practice and demonstrate possible ways to solve the problem of AP-induced LQTS in a young man with paranoid Sch.

Methods

Procedure

PGx was used based on the pharmacogenetic profile of patients with mental disorders (homo- and heterozygous carriers of risk alleles of low-functional and non-functional SNVs of the *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP1A2* and *CYP3A4* genes encoding cytochrome P450 enzymes involved in APs metabolism, and SNV of the MDR1 (ABCB1) gene encoding transport protein P-glycoprotein (P-gp). Pharmacogenetic testing (PGx) was carried out using real time polymerase chain reaction (RT-PCR), while the cumulative risk of developing AP-induced ADRs was assessed due to impaired 1th, 2nd and 3rd generations APs.

Ethical Aspects

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. The clinical approbation was carried out within the framework of the state order. The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical trial. Researchers did not receive any remuneration for conducting clinical trials.

Results

Life History

The patient was born in Leningrad, in a family of hearing-impaired parents. Mother died in November 2019. There are 2 younger brothers. The patient attended a kindergarten, speech therapy group. He went to school for 8 years. Duplicated 1 and 5 classes. From the 7th grade, he periodically did not attend classes at school. Graduated from 9 classes. Later he worked as a laborer. By nature, the patient is timid, shy, unbalanced. He served in the army, but was released from service due to the development of a mental disorder. After demobilization, the patient often changed jobs, worked as a bartender, in a bakery, in a pet store. He spent his free time in nightclubs. Not married, no children. The patient lived in a separate apartment alone, sometimes with acquaintances from the hospital where he had previously been treated. In the last two years he lived with his family in a separate apartment.

Medical History

Sch was first diagnosed in 2004. Inpatient treatment was recommended, a therapeutic effect was achieved against the background of APs therapy. The condition worsened in 2008, when psychosis developed, delusions of persecution, delusions of relationship, which led to hospitalization. After 14 months of therapy with haloperidol and azaleptin, positive dynamics was achieved, the patient was discharged under the supervision of a psychiatrist at the place of residence in 2010.

Subsequently, the patient was repeatedly hospitalized in the psychiatric hospital of St. Nicholas the Wonderworker (St. Petersburg) with paraphrenic symptoms. Behavioral

disorders, alcohol dependence, cannabis smoking later appeared. Last hospitalization in 2019 due to suicide attempt. On the background of APs therapy, the positive symptoms of Sch were stopped, tension and anxiety decreased, but the patient's criticism of his condition remained reduced. Painful experiences decreased, but did not stop. In a conversation, the patient voiced that he had a special gift of foresight. In November 2019, the patient's condition changed after receiving the news of his mother's death. He reported that he saw prophetic dreams about her death, and as a gifted one, he was obliged to prevent what happened. After titrating the dose of AP, the mental state improved. From December 2019 to the present, the patient has been treated at the psychiatric hospital of St. Nicholas the Wonderworker (Saint Petersburg) with persistent delusional symptoms.

Mental Status

1) At Time of Admission to St. Nicholas Psychiatric Hospital

Consciousness is not clouded. Oriented all around. The physique is asthenic, the posture is stooped, the appearance is not neat. Attention is passive, unstable. The gait is confident, the movements are expressive, tense. Gesticulation is mannered, pretentious. Paramimic, emotionally flattened, anxiety predominates. Speech is fast, emotional, spontaneous, mannered, vocabulary is poor. Attitude towards the conversation is friendly, interested, actively seeks the conversation. Answers to questions are verbose. Thinking is not consistent with atactic closures. He "possesses the gift of foresight", "sees prophetic dreams". Severe memory disorders were not identified. General education and cultural levels are insufficient. Criticism towards statements and disease has been reduced. Predictive ability reduced. Did not voice suicidal thoughts.

2) At the Time of Inclusion in the Study

Consciousness is not clouded. The patient is oriented in the environment correctly. Ordered in behavior, obedient to the regime, passive, isolated, autistic, contactable. The patient is calm in conversation, speech periodically acquires the character of a monologue. Thinking with ataxia, resonant. The mood is even. Emotionally inexpressive, mimic reactions are stereotyped. Deceptions of perception denies. Delusional symptoms deactualized, no effect on behavior. Did not voice suicidal thoughts.

Clinical Diagnosis

Main: Paranoid schizophrenia, continuous course, incomplete remission.

Concomitant: Mild protein-energy malnutrition. Iron deficiency anemia, unspecified, mild. Diaphragmatic hernia without obstruction or gangrene. Duodenal ulcer, not specified as acute or chronic, without bleeding or perforation. Gastroesophageal reflux without esophagitis. Gastritis unspecified.

Conducted Therapy

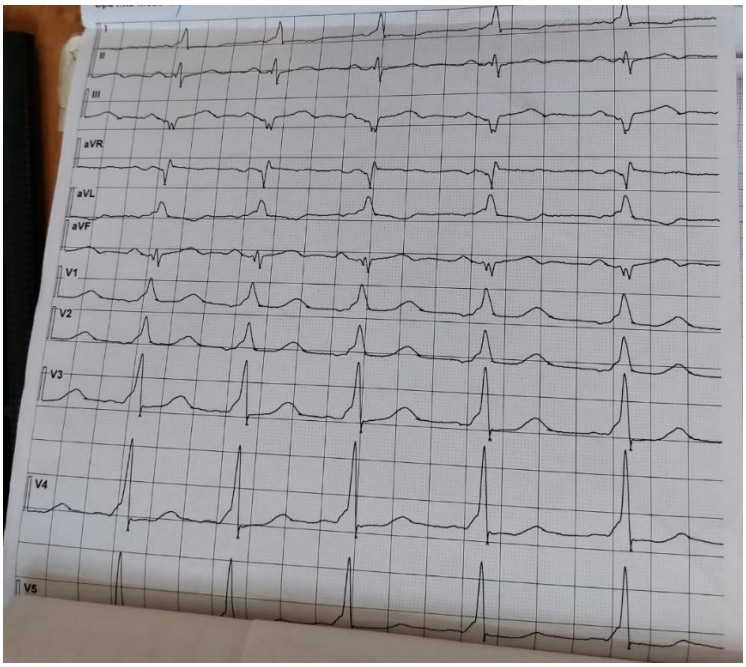
During the period of inpatient treatment, the patient was treated with the following APs:

- Olanzapine 0.01 g per day, followed by an increase in dose to 0.02 g per day;
- Risperidone 0.002 g per day, followed by a dose change to the maximum daily dosage (MDD) of 0.005 g;
- Quetiapine 0.3 g per day, then increased to 0.4 g per day;
- Haloperidol 0.5% - 1.0 IM followed by a dose change to MDD 3.0 ml per day;
- Haloperidol decanoate 2.0 (100 mg) IM once every 2 weeks;
- Haloperidol 0.015 g per day;
- Chlorpromazine 0.1 g per day;
- Clozapine 0.025 g per day, followed by an increase in dose to 0.4 g per day, followed by a dose reduction to 0.6 g per day;

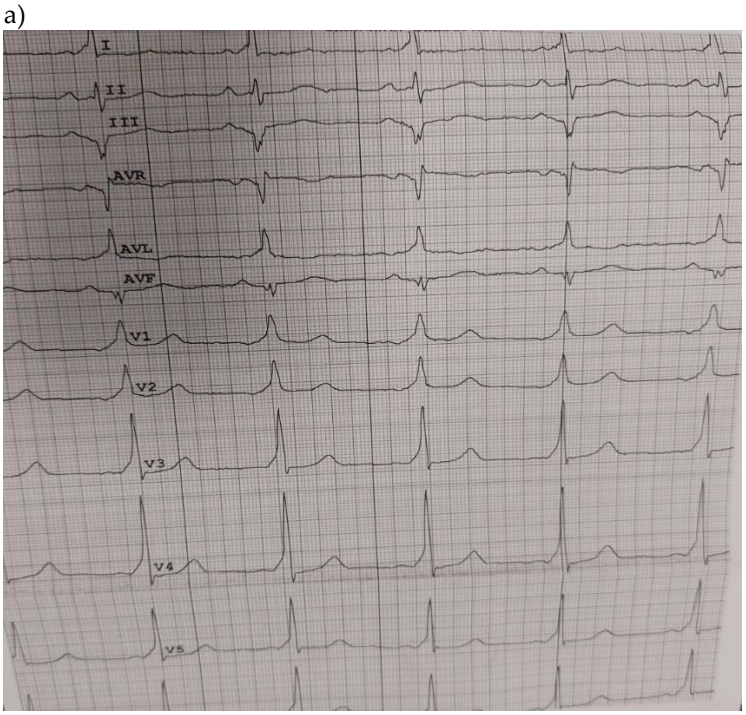
- Zuclopenthixol 0.001 g 2 times a day, followed by an increase in dose to 0.04 g MDD.

Electrocardiogram

During the period of treatment in a psychiatric hospital in a hospital, the ECG showed a slowly progressive prolongation of the QT interval (**Figure 1**) against the background of antipsychotic therapy, but without a clear dependence on a specific APs.



a)



в)

Figure 1. Electrocardiogram of a 36-year-old patient with paranoid schizophrenia on the background of polytherapy with antipsychotics: a) QTc = 0,45; в) QTc = 0,46

Pharmacogenetic Testing

According to the results of pharmacogenetic testing, it was revealed that the patient is an intermediate metabolizer for CYP2D6 and a carrier of the low-functional allele T (**Table 1**), the gene encoding this isoenzyme of liver cytochrome P450.

Table 1. The result of pharmacogenetic testing

Gene, OMIM	Chromosomal location	SNVs	Genotype	Evaluation of the result
CYP2D6 608902	22q13.2	rs4986774 rs1065852 rs3892097	A/A C/C **G/A!**	Abnormal. Hererozygous carrier of the non-functional allele A. Poor metabolism of APs in the liver.
CYP2C9 601130	10q23.33	rs1799853 rs1057910	C/C A/A	Normal. Extensive metabolism of AP in the liver.
CYP2C19 609535	10q23.33	rs4244265 rs4986893 rs28399504	G/G G/G A/A	Normal. Extensive metabolism of AP in the liver.
CYP3A4 124010	7q22.1	rs4987161 rs28371759 rs2740574	T/T T/T A/A	Normal. Extensive metabolism of AP in the liver.
MDR1 171050	7q21.12	rs1045642	C/T!	Abnormal. Heterozygous carrier of the non-functional T allele - delayed efflux of APs across the blood-brain barrier with the participation of the P-gp transporter protein.

Table 1 demonstrates that the patient was found to be heterozygous carrier of the minor allele A of the non-functional SNV rs3892097 (G/A genotype - substitution of guanine for adenine). This explains the slowdown in metabolism by about 40-50% of such APs as olanzapine, risperidone, quetiapine, chlorpromazine, clozapine, zuclopenthixol [4, 5] that the patient we observed was taking. In addition, the patient was found to be a heterozygous carrier of the minor allele T of the low-functional SNV rs1045642 (C/T genotype - replacement of cytosine by thymine) [5]. Thus, for the first time, a genetic biomarker for a decrease in the functional activity of the transport protein glycoprotein P (P-gp), which is involved in the APs efflux through the histohematological barriers and the membrane of neurons and cardiomyocytes, was detected in the patient for the first time. This may explain the neuro- and cardiotoxic effects of a wide range of APs, including those taken by the patient.

A cumulative assessment of the risk of developing QT interval prolongation in our patient showed that the most unfavorable in relation to arrhythmogenic ADRs of this APs therapy are: olanzapine, risperidone, quetiapine, chlorpromazine, clozapine, zuclopenthixol. Low risk of QT interval prolongation with haloperidol deconoate and cariprazine.

The uniqueness of the presented clinical case lies in the fact that in a 36-year-old man with Sch clinical symptoms of cardiac AP-induced ADRs prevail over possible neurotoxic AP-induced ADRs. This suggests that the patient is likely to be a carrier of SNV/polymorphisms of candidate genes predisposing to the development of multifactorial forms of LQTS, including the *HERG, SCN5A, KCNE1/MIRP1* и *AKAP9/KCNQ1* genes, and/or a heterozygous carrier of mutations in the causal genes responsible for autosomal dominant familial forms of LQTS (*KCNQ1, KCNH2/HERG, ALG10B, SCN5A, ANK2, KCNE1/MIRP1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9/KCNQ1, SNTA1, KCNJ5, CALM1, CALM2, CALM3*) [3].

Unfortunately, we were unable to find a family history of LQTS in the pedigree, however, the patient testified to the absence of cases of SDS in his family members.

Conclusion

AP-induced LQTS is a potentially life-threatening AP-induced ADRs in patients with schizophrenia. This problem is being actively studied, but is far from being resolved. Despite the alertness of psychiatrists and the hospital to diagnose this ADRs, there is no

possibility of genetic screening for familial and multifactorial forms of LQTS, and there is also no possibility of pharmacogenetic testing in most institutions.

The development of personalized medicine and pharmacogenetics prompts us to reconsider outdated views on AP-induced ADRs and actively introduce modern methods of DNA profiling into the real clinical practice of a psychiatrist. A personalized approach to assessing the risk of APs efficacy and safety may reduce the risk of cardiotoxic AP-induced ADRs, including AP-induced LQTS, and thus reduce the risk of SDS in patients with Sch.

The authors believe that it is desirable to carry out pharmacogenetic testing before the start of taking a specific APs, and not with the development of a potentially life-threatening ADRs. However, in the presented clinical case, pharmacogenetic testing after the development of AP-induced LQTS made it possible to review Sch APs therapy in a young patient and cancel "dangerous" APs, thereby reducing the risk of SDS.

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