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Personalized Psychiatry and Neurology

Case Report

The Role of Pharmacogenetic Testing in Overcoming Pseudoresistance and Hyperprolactinemia in a 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 drug reactions. Approximately 20-30% of patients with schizophrenia remain resistant to psychopharmacotherapy. Determining the individual predisposition to the response to antipsychotics and antipsychotic-induced adverse drug reactions development is possible using pharmacogenetic testing. **Purpose** is to present the role of pharmacogenetic testing in optimizing antipsychotic therapy. **Materials and methods:** The peripheral blood of patients was genotyping using real-time polymerase chain reaction. **Results**: This case report is about a 30-year-old female patient with paranoid schizophrenia, which had a long history of low effectiveness and poor tolerability of antipsychotics. The treatment was complicated by the pituitary microadenoma presence. According to the PGx results, the patient has a "poor transporter" phenotype, which also explains the high risk adverse drug reactions developing and therapeutic resistance while taking P- glycoprotein substrates antipsychotics. For the treatment, the antipsychotic brexpiprazole was selected, which did not have the P-glycoprotein substrate properties. It made possible to achieve paranoid schizophrenia remission and hyperprolactinemia correction. **Conclusion:** This case report demonstrates that wider implementation of pharmacogenetic testing into real clinical practice could help significantly improve the efficiency and safety of antipsychotic therapy.

Keywords: *pharmacogenetic testing; antipsychotic; transporter; p-glycoprotein; brexpiprazole; psychopharmacotherapy*

1. INTRODUCTION

Schizophrenia is an important socially significant mental illness due to the early onset, rapid social decompensation and a high patient disability [1, 2]. Despite the new antipsychotics development, approximately 20-30% of patients with schizophrenia remain resistant to psychopharmacotherapy [3]. The problem of antipsychotic-induced adverse drug reactions (ADRs) also remains unresolved [4].

Approximately a quarter of the total variability in response to antipsychotics is genetic in origin [5]. Genetic predisposition to the antipsychotic-induced ADRs development is caused by single-nucleotide variants polymorphism (SNP) of genes encoding proteins involved in the antipsychotics metabolism and transport [6]. Important factor in ensuring an optimal balance between the therapy effectiveness and safety is the timely detection of genetically determined disorder transporter proteins work ensure the antipsychotics efflux (transport from the brain to the blood) [7].

Determining the individual genotype characteristics is possible using pharmacogenetic testing (PGx) [8]. Pro-reactive PGx is recommended before prescribing an antipsychotic [9]. Reactive PGx is used in patients who have a long ADRs history or treatment resistance [10].

Purpose of this case report is to present the role of pharmacogenetic testing in in improving the efficacy and safety of antipsychotic therapy.

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 patient was observed at the Institute of Personalized Psychiatry and Neurology of Bekhterev National Medical Research Center for Psychiatry and Neurology of the Ministry of Health of the Russian Federation.

2.2. Procedure

Patients were recruited for genotyping using real-time polymerase chain reaction (PCR) at the Laboratory of Molecular Genetic Diagnostics of the Institute of Personalized Psychiatry and Neurology of Bekhterev National Medical Research Center for Psychiatry and Neurology of the Ministry of Health of the Russian Federation.

The study material was sample the peripheral blood of patient collected in VACUETTE® vacuum tubes (Greiner Bio-One, Kremsmünster, Austria). A standard method of DNA extraction was used. Genomic DNA was isolated from the nuclei of peripheral blood leukocytes using the DNA-Extran-1 kit (Syntol, Moscow, Russia). The PCR was performed with negative control. The primers were designed using PrimerSelect 4.05©1993–2000 DNASTAR Inc. software and synthesized by Syntol. Carriage of SNPs was determined by real-time PCR with the SNP-Screen kit from ZAO Syntol. The program included preliminary denaturation at 95°C lasting 3 minutes, 40 cycles of denaturation at 95°C for 15 seconds per cycle, and then annealing at 60°C for 40 seconds using Real-Time CFX96 Touch (Bio-Rad Laboratories Inc., Hercules, CA, USA).

2.3 Ethical considerations

The study was conducted in accordance with the standards of clinical practice and the principles of the Declaration of Helsinki. The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical study.

3. RESULTS

The case involves a 30-year-old woman. There is no data on hereditary burden. Born full term. Development by age. Higher education. She has not worked over a year. Lives with a partner. There is no history of smoking, alcohol, or substance use.

Mental disorders for several years. She began to notice her mother was harming her, feel “oxygen lack”. She noticed the colleague was “stalking” her. So she consulted a psychiatrist.

After the examination, was diagnosed with paranoid schizophrenia, she started taking risperidone. Due to drowsiness, she was switched to paliperidone, but

amenorrhea and galactorrhea appeared. The prolactin level was 4000 mU/l. Magnetic resonance imaging revealed a microadenoma of the pituitary gland. She took cabergoline as prescribed by the endocrinologist. She was switched to quetiapine 600 mg/day. After that, mood instability and increased tension appeared due to the feeling an energetic influence on her. She also felt a openness of thoughts.

Due to this she was hospitalized. Received therapy: aripiprazole up to 30 mg/day, then ziprasidone up to 160 mg/day, discontinued due to ineffectiveness; clozapine 50 mg/day, canceled due to delirium, haloperidol up to 20 mg/day, trifluoperazine up to 35 mg/day, canceled due to insufficient effectiveness, extrapyramidal syndrome, increase in prolactin level to 1300 mU/l. Then the patient received cariprazine up to 6 mg/day. And 7 sessions of electroconvulsive therapy were performed. The mental state remained unstable. Paranoid symptoms and social decompensation persisted.

To personalize the antipsychotic therapy, the patient underwent PGx (Table 1).

Tabel 1. Results of reactive pharmacogenetic testing.

Index	**Single-nucleotide variant**	**Position**	**Genotype**	**Result**
Analysis of common genetic variants in the *CYP2C9* gene (2 polymorphisms). PCR method, sequencing	rs1799853 (430C>T) rs1057910 (1075A>C)	chr10:94942290 (GRCh38.p14) chr10:94981296 (GRCh38.p14)	C/C A/A	Normal, homozygous carrier of fully functional alleles C and A, pharmacogenetic profile is extensive metabolizer
Analysis of common genetic variants in the *CYP2C19* gene (3 polymorphisms). PCR method, sequencing	rs4244285 (CYP2C19*2, 681G>A) rs4986893 (CYP2C19*3, 636G>A) rs28399504 (CYP2C19*4, 1A>G)	chr10:94781859 (GRCh38.p14) chr10:94780653 (GRCh38.p14) chr10:94762706 (GRCh38.p14)	G/G G/G A/A	Normal, homozygous carrier of fully functional alleles G, G and A, pharmacogenetic profile is extensive metabolizer
Analysis of common genetic variants in the *CYP2D6* gene (2 polymorphisms). PCR method, sequencing	rs1065852 (CYP2D6*10, 4300C>T) rs3892097 (CYP2D6*4, 6047G>A)	chr22:42526694 (GRCh37p.14) chr22:42128945 (GRCh38.p14)	C/C G/G	Normal, homozygous carrier of fully functional alleles C and G, pharmacogenetic profile is extensive metabolizer
Analysis of common genetic variants in the *CYP3A4* gene (3 polymorphisms). PCR method, sequencing	rs4987161 (CYP3A4*17, 15624C>T) rs28371759 (CYP3A4*18, 20079C>T) rs2740574 (CYP3A4*1B, -392A>G)	chr7:99768458 (GRCh38.p14) chr7:99764003 (GRCh38.p14) chr7:99784473 (GRCh38.p14)	T/T T/T A/A	Normal, homozygous carrier of full-function T, T and A alleles, pharmacogenetic profile is extensive metabolizer
Analysis of common genetic variants in the *CYP1A2* gene (1 polymorphism). PCR method, sequencing	rs2069522 (1952T>C)	chr15:75039233 (GRCh38.p14)	T/T	Normal, homozygous carrier of fully functional T allele, pharmacogenetic profile is extensive metabolizer
Analysis of common genetic variants in the *ABCB1* gene (1 polymorphism). PCR method, sequencing	**rs1045642 (3435C>T)**	**chr7:87509329 (GRCh38.p14)**	**T/T!**	**Homozygous carrier of the non-functional T allele, pharmacogenetic profile is poor transporter**

Note: *PCR – polymerase chain reaction; CYP2C9 - isoenzyme 2C9 of cytochrome p450; CYP2C19 - isoenzyme 2C19 of cytochrome p450; CYP2D6 – isoenzyme 2D6 of cytochrome p450; CYP3A4 - isoenzyme 3A4 of cytochrome p450; CYP1A2 - cytochrome p450 isoenzyme 1A2; ABCB1 is a type 1 multidrug resistance gene.*

In screening PGx with detection the most common non-functional SNPs of the *CYP2C9, CYP2C19, CYP1A2, CYP3A4* and *CYP2D6* genes, encoding the activity of the liver cytochrome P450 isoenzymes 2C9, 2C19, 1A2, 3A4 and 2D6, and the *ABCB1* gene, encoding the transport protein P-glycoprotein (P-gp), homozygous carriage of the non-functional T allele rs1045642 of the ABCB1 gene was revealed. It is associated with a pronounced slowdown in the P-gp substrates efflux. It was established the patient has a "poor transporter" pharmacogenetic profile.

The patient was consulted by a clinical pharmacologist. Cabergoline avoidance and other dopamine receptor agonists is recommended. It is recommended to consult a neurosurgeon for surgical pituitary microadenoma treatment.

Due to the "poor transporter" phenotype, the patient was recommended to discontinue cariprazine. It was recommended to use with great caution P-gp substrates drugs. In monotherapy mode: it was recommended to reduce the starting and target doses by at least 50%. In polytherapy mode - by at least 75% when taken simultaneously drugs with similar transport or not to use such combinations. The use of P-gp inhibitors drugs and nutrients is not recommended. The use of P-gp inducers drugs is permitted.

The patient was prescribed brexpiprazole. A marked improvement in the condition was achieved: anxiety and paranoid symptoms were relieved, the negative symptoms decreased. The prolactin level decreased to 550 mU/l. The patient was discharged home in satisfactory condition with a recommendation to continue taking brexpiprazole 3 mg/day.

For six months after discharge, the patient's condition remains satisfactory, there are no psychoproductive symptoms, and no ADRs are registered. The patient got a job, communicates with relatives, successfully manages housework.

4. DISCUSSION

In this case report, the patient with schizophrenia had a long history of low effectiveness and poor tolerability of antipsychotics. The treatment was complicated by the pituitary microadenoma presence, which contributes to hyperprolactinemia, as well as concomitant therapy with cabergoline to relieve this symptom [11]. Cabergoline may cause or intensify hallucinations and delusions in the patient due to high dopaminergic activity in the brain mesolimbic pathway. This may have increased treatment resistance of psychotic symptoms to antipsychotic treatment.

According to the PGx results, the patient has a "poor transporter" phenotype, which also explains the high risk ADRs developing and therapeutic resistance while taking P-gp substrates antipsychotics. P-gp is a membrane transport protein with a wide range of substrates [12]. It is encoded by the *ABCB1* gene, which is highly polymorphic [13].

It became known the patient is a homozygous carrier of the non-functional allele rs1045642 of the *ABCB1* gene, which is one of the most common non-functional single-nucleotide variants of this gene in the European population. For the treatment, the antipsychotic brexpiprazole was selected, which did not have the P-gp substrate properties [14]. And it made possible to achieve paranoid schizophrenia remission and hyperprolactinemia correction [15].

The pro-reactive PGx use would make possible to predict antipsychotics likely ADRs, taking into account individual metabolism and transport characteristics, and initially prescribe the most appropriate psychopharmacotherapy [16]. In this way, it would be possible to avoid the antipsychotic-induced ADRs, reduce the economic costs of using undesirable for the patient medications and for staying in a hospital [17, 18].

5. CONCLUSION

This case report convincingly demonstrates wider PGx implementation and a personalized approach to psychopharmacotherapy in clinical practice can help significantly improve the effectiveness and safety of antipsychotic therapy.

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