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Case report

APPLICATION OF PHARMACOGENETICS IN THE PERSONALIZED TREATMENT OF A PATIENT WITH HYPOCHONDRIASIS: CASE REPORT

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Abbreviations: *PGT - pharmacogenetic testing; CYP – cytochrome; BBB - blood-brain barrier; DSM-5 - diagnostic and statistical manual of mental disorders, fifth edition; ICD-10 - international statistical classification of diseases and related health problems 10th revision; SNVs - single nucleotide variants; P-gp - P-glycoprotein*

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INRODUCTION

According to epidemiological data, hypochondriac disorder (now known as illness anxiety disorder) has a high prevalence in the general population is high, ranging from 4.5 to 20% (Creed & Barsky 2004). Treating this condition remains a complex medical challenge, and we lack definitive treatment guidelines. Hypochondriac disorder is often managed with a combination of antidepressants and low-dose antipsychotic medications, or in a comprehensive therapy that also includes anxiolytics (Shestakova et al. 2022). The concurrent use of multiple medications is common, despite the increased risk of adverse reactions. Poor drug tolerance and insufficient clinical efficacy reduce patient adherence to therapy, prolonging the illness and increasing the burden on healthcare systems and society (Semahegn et al. 2020).

An important factor determining the response to any pharmacotherapy is individual pharmacokinetic and pharmacodynamic variability. Common functional variants of genes encoding metabolic enzymes, transporter proteins, and therapeutic targets of medications play a role in interindividual differences in treatment response. Most antidepressants and antipsychotics are metabolized by cytochrome P450 enzymes in the liver, such as CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP1A2. These enzymes have become central to the clinical application of pharmacogenetics in psychiatry due to the close relationship between genetic variants and enzymatic activity (van Schaik et al. 2020). The MDR1 gene encodes the P-gp transporter positioned in the blood-brain barrier (BBB). Since antidepressant and antipsychotic medications are often substrates for P-gp, MDR1 polymorphisms can influence their access to the brain, consequently influencing their therapeutic effects, and side effects (Magarbeh et al. 2023).

Thus, PGT can provide crucial data that influence the optimal choice and dosage of medication. Finding the most effective dose with minimal side effects is a critical step towards personalized therapy (Whirl-Carrillo et al. 2021). In this clinical case report of a patient suffering from hypochondriac disorder, we illustrate the importance of considering pharmacogenetic data and recommendations based on these data in clinical practice. The application of pharmacogenetic insights successfully altered the course of previously ineffective treatment.

CASE DESCRIPTION

A 62-year-old Caucasian male, diagnosed with hypochondriasis (DSM-5: 300.7, ICD-10: F45.2), was referred by a hospital psychiatrist for PGT due to the lack of effect and development of adverse reactions from his ongoing pharmacotherapy. According to his medical history, the patient had been receiving a variety of psychopharmacological medications (olanzapine, amisulpride, fluoxetine, fluvoxamine, sertraline, citalopram, clomipramine, valproic acid, carbamazepine) at average therapeutic doses, both as monotherapy and in various combinations, for the past twenty years, without obtain ing sufficient clinical benefits, and with the development of certain adverse reactions.

At the time of PGT, his therapy included paroxetine 40 mg/day and chlorprothixene 25 mg/night, with concomitant medication with tamsulosin 400 mcg/day for benign prostatic hyperplasia. The patient was a non-smoker and did not consume coffee. During medication treatment, he reported persistent headaches, dizziness, drowsiness, anxiety, paresthesias, and arterial hypotension. The treating physician faced difficulties in distinguishing these symptoms as being adverse reactions to the medication therapy or as persistent hypochondriacal symptoms.

During screening of PGT for the most common low-functioning and non-functional single nucleotide variants (SNVs) in the genes CYP2C9, CYP2C19, CYP1A2, CYP3A4, CYP2D6, which encode the activity of liver cytochrome P450 isoenzymes 2C9, 2C19, 1A2, 3A4, and 2D6, respectively, as well as in the MDR1 gene encoding the P-gp transporter, there emerged several findings that were relevant for a patient of European descent. In particular, the screening identified heterozygous carriage of the non-functional C rs1057910 allele of the CYP2C9 gene, heterozygous carriage of the non-functional A rs4244285 allele of the CYP2C19 gene, and heterozygous carriage of the non-functional T rs1045642 (C3435T) allele of the MDR1 (ABCB1) gene. These alleles are among the most commonly encountered non-functional SNVs in these genes within the European population. The patient's pharmacogenetic profile was identified as corresponding to an intermediate metabolizer and an intermediate transporter (Table 1). We assessed a high cumulative risk of developing adverse reactions and pseudo-resistance during treatment with medications metabolized in the liver by the CYP2C9 and CYP2C19 cytochrome P450 enzymes and transported by the P-gp transporter. The identified genetic markers are associated with moderately reduced metabolism of certain psychotropic medications in the liver, and moderately reduced efflux from brain to blood, this predicting elevated drug levels in brain.

Paroxetine is primarily metabolized in the liver via the cytochrome P450 2D6 enzyme (Bloomer et al. 1992, Kaye et al. 1989), whereas experiments in vitro suggest that cytochrome P450 enzymes CYP1A2 and CYP3A4 play a minor role in the metabolism of paroxetine (Jornil et al. 2010). We did not detect any common low-functioning SNVs in genes CYP2D6, CYP1A2, and CYP3A4 in the patient, predicting no impairments in the metabolism of paroxetine. The transport of paroxetine at the BBB involves the P-gp transporter protein (Weiss et al. 2003). The patient's heterozygous carriage of the low-functioning T allele of the rs1045642 variant in the MDR1 gene would likely lead to moderate slowing of paroxetine efflux from the brain to the blood, and a consequently increased risk of developing neurotoxic disorders (Kato et al. 2008). This vulnerablity may explain the patient’s adverse reactions, such as headaches, dizziness, drowsiness, anxiety, paresthesias, and poor response to therapy. We recommended a 50% paroxetine dose reduction relative to the average therapeutic dose when prescribed in polytherapy or for prolonged courses (more than 3 months), especially when combined with other substrates or inhibitors of the P-gp transporter protein.

Simultaneous administration of paroxetine and tamsulosin poses a risk of drug-drug interaction. The metabolism of tamsulosin may be reduced when combined with paroxetine, as the two drugs are competing substrates/inhibitors for the same hepatic enzyme, CYP2D6 (Kowalska et al. 2021). This combination can lead to increased tamsulosin concentrations in the blood serum and the development of tamsulosin-induced adverse reactions such as arterial hypotension, tachycardia, and dizziness. Therefore, concurrent use of paroxetine and tamsulosin is not recommended for this patient. We recommended switching tamsulosin to dutasteride, given its predominant metabolism through CYP3A4.

Chlorprothixene is primarily metabolized in the liver, with the predominant involvement of the CYP2D6 isoenzyme (Spina & de Leon 2015). The patient does not exhibit common low-functional SNPs in the CYP2D6 gene, which encodes the aforementioned enzyme. Drugs that inhibit the CYP2D6 enzyme (such as paroxetine) may increase the chlorprothixene concentration in the bloodstream and contribute to the development of adverse reactions. Chlorprothixene itself acts as an inhibitor of the P-gp transporter protein (Bader et al. 2008), which is relevant when concurrently used with paroxetine in this patient. Considering the heterozygous carriage of the low-functional T allele variant rs1045642 in the MDR1 gene, which leads to a slowing of paroxetine efflux from the brain to the blood and an increased risk of neurotoxic effects, the combination with chlorprothixene (a P-gp inhibitor) is not recommended in this case (Table 1).

DISCUSSION

The presented clinical case highlights the importance of understanding a patient's pharmacogenetic profile before initiating psychopharmacotherapy. Pharmacogenetic testing can assist in selecting the safest pharmacotherapy options, promoting improved treatment response, achieving rapid remission, and/or reducing the risk of treatment-related toxicity (Strelnik et al. 2023).

The patient suffering from hypochondriacal disorder, while under treatment with paroxetine 40 mg/day and chlorprothixene 25 mg, along with concurrent medication of tamsulosin 400 mcg/day. He obtained little relief from psychiatric symptoms, but reported troubling side effects including headache, dizziness, drowsiness, increased anxiety, paresthesia, and arterial hypotension. The indications for conducting PGT in this case included a prolonged history of ineffective treatment and challenges in distinguishing the various symptoms as adverse reactions to pharmacotherapy or persistent hypochondriacal symptoms.

Table 1. Results of the pharmacogenetic testing

Name/indicator	Single-nucleotide variant (NCBI SNP, allelic variant)	Genotype	Estimation
Analysis of the frequent genetic variants in CYP2C9 gene (2 polymorphisms). PCR method, sequencing.	rs17998553 (C430T, Cys144Arg) rs1057910 (Ile359Leu, A1075C)	C/C A/C	A heterozygous carrier of the non-functional C allele indicates an intermediate metabolizer pharmacogenetic profile (IM)
Analysis of the frequent genetic variants in CYP2C19 gene (3 polymorphisms). PCR method, sequencing.	rs4244285 (CYP2C19*2) rs4986893 (CYP2C19*3) rs28399504 (CYP2C19*4)	G/A G/G A/A	A heterozygous carrier of the non-functional A allele indicates an intermediate metabolizer pharmacogenetic profile (IM)
Analysis of the frequent genetic variants in CYP2D6 gene (3 polymorphisms). PCR method, sequencing.	rs4986774 (CYP2D6*3A) rs1065852 (CYP2D6*10) rs3892097 (CYP2D6*4)	A/A C/C G/G	Norm, pharmacogenetic profile extensive metabolizer (EM)
Analysis of the frequent genetic variants in CYP3A4 gene (3 polymorphisms). PCR method, sequencing.	rs4987161 (CYP3A4*17) rs28371759 (CYP3A4*18) rs2740574 (CYP3A4*1B)	T/T T/T A/A	Norm, pharmacogenetic profile extensive metabolizer (EM)
Analysis of the frequent genetic variants in CYP1A2 gene (1 polymorphism). PCR method, sequencing.	rs2069522	T/T	Norm, pharmacogenetic profile extensive metabolizer (EM)
Analysis of the frequent genetic variants in MDR1 gene (1 polymorphism). PCR method, sequencing.	rs1045642 (C3435T)	T/C	A heterozygous carrier of the non-functional T allele indicates an intermediate transporter pharmacogenetic profile (IT).

The presented patient is a carrier of the non-functional allele C rs1057910 of the CYP2C9 gene, heterozygous carrier of the non-functional allele A rs4244285 of the CYP2C19 gene, and heterozygous carrier of the non-functional allele T rs1045642 (C3435T) of the MDR1 gene. Considering the impact of these genetic variants on the effectiveness and tolerability of the patient's pharmacotherapy, we recommended adjustments to the medication regimen: paroxetine was reduced to 20 mg/day, chlorprothixene was discontinued, and tamsulosin was replaced with dutasteride. Following these adjustments, the patient's mental state improved. In the subsequent two weeks, complaints of headache, dizziness, drowsiness, anxiety, paresthesia, and arterial hypotension all but disappeared.

In the presented case, we have demonstrated how consideration of a patient's pharmacogenetic characteristics can improve treatment outcomes and patient well-being. Knowledge of the patient's pharmacogenetic profile helped us personalize the treatment, leading to an improvement in their mental state.

In pharmacogenetic studies of cytochrome enzyme gene alleles, not all results align perfectly with expectations based on previous literature (Maggo et al. 2019). Therefore, it is crucial to conduct additional pharmacokinetic and pharmacogenetic studies to better assess the interaction between genes and medications. This knowledge will inform the rational adjustment of dosages and combinations of prescribed drugs to obtained personalize treatment with enhanced safety and effectiveness.

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Conflict of interest:

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Contribution of individual authors:

Anna Strelnik & Regina Nasyrova: search and analysis of literature, collection of clinical data, data interpretation, drafting of the first draft.

Sergey Strelnik, Kseniya Bikbaeva, Natalia Kuvshinova & Dmitry Romanov: search and analysis of literature, data interpretation, and editing.

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