Personalized Psychiatry and Neurology

Case report

Antipsychotic-Induced Parkinsonism and Dyskinesia in a 43-years Old Male with Schizophrenia: Clinical Case

Elena E. Vaiman[1*] and Lidia P. Linova[2]

[1] Institute of Personalized Psychiatry and Neurology, V. M. Bekhterev National Medical Research Center for Psychiatry and Neurology, St.-Petersburg, Russia;
[2] P.P. Kashchenko Psychiatric Hospital No1, Nikolskoe, St. Petersburg, Russia;
* Correspondence: e-mail: vaimanelenadoc@gmail.com (E.E.V.); Tel.: +7-(812)-670-02-20

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Abstract: The development of neurological adverse drug reactions (ADRs) from the extrapyramidal system while taking antipsychotics (APs) is well known. The common forms of neurological ADRs from the side of the extrapyramidal system are AP-induced parkinsonism (AIP) with a frequency of about 36% and AP-induced tardive dyskinesia (AITD) with an incidence of about 25%. Patients with AIP and AITD make up a significant proportion of patients in psychiatric hospitals and neuropsychiatric dispensaries with AP-induced extrapyramidal disorders requiring neurological care. These ADRs make a significant contribution to the structure of the overall morbidity and mortality of the population around the world. We presented a clinical example of 43 years old male, who developed acute AIP and AITD while taking APs. This condition was resolved with amantadine 200 mg/day after several unsuccessful attempts. It is also known that the patient had a father with Parkinson's disease in his anamnesis. The patient underwent pharmacogenetic testing of SNV rs1800497 of the *DRD2* gene. According to the results the patient was a homozygous carrier of the major allele. These results did not show a positive association. At the same time, such a patient needs to undergo pharmacogenetic testing using a complete genetic risk panel for developing AIP, AITD, and Parkinson's disease.

Keywords: *antipsychotics; extrapyramidal system; antipsychotic-induced parkinsonism; antipsychotic-induced tardive dyskinesia; amantadine; gene DRD2; pharmacogenetic testing*

Introduction

The development of neurological adverse drug reactions (ADRs) from the extrapyramidal system while taking antipsychotics (APs) is well known [1]. Despite the emergence of new generations of AP, the problem of the development of ADRs from the extrapyramidal system remains relevant and reduces the patient's compliance with AP due to stigmatization and the development of disability. The common forms of neurological ADRs from the side of the extrapyramidal system are AP-induced parkinsonism (AIP) with a frequency of about 36% [2] and AP-induced tardive dyskinesia (AITD) with an incidence of about 25% [3]. Patients with AIP and AITD make up a significant proportion of patients in psychiatric hospitals and neuropsychiatric dispensaries with AP-induced extrapyramidal disorders requiring neurological care. These ADRs make a significant contribution to the structure of the overall morbidity and mortality of the population around the world. [4]. For many years, the comorbidity of AP-induced extrapyramidal disorders, in particular AIP and AITD, and schizophrenia

spectrum disorders has been considered as a state of mutual aggravation or crossover syndrome [5].

Objective

The main purpose is to provide a clinical case of antipsychotic-induced crossover syndrome of extrapyramidal disorders (AIP and AITD) using pharmacogenetic testing (PGx).

Methods

Procedure

PGx was used based on the pharmacogenetic profile of patients with psychiatric disorders (homo- and heterozygous carriage risk alleles of single nucleotide variant (SNV) rs1800497 (NG_012976.1:g.17316G>A) of candidate gene *DRD2*, encoding dopaminergic receptor types 2 and 3). PGx was performed using real-time polymerase chain reaction (RT- PCR), with the development of ADRs caused by APs, was assessed due to APs of the 1st, 2nd and 3rd generations.

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

Patient R., 43 years old is a native of Leningrad. He was born the only child in the family. There are no data on aggravated psychopathological heredity. The patient notes that the father suffered from Parkinson's disease. Parents have now died of cardiovascular disease. The patient developed according to age. He attended a children's school and was adapted. I went to school from the age of 7. He studied well. There were friends at school and no conflicts with students and teachers. The patient graduated from the 9th grade of a general education school. Then he studied at a radio engineering college, but left his studies, as it seemed to him “too simple”. Then he studied at the courses of builders, worked in City Dentistry No. 1 as a builder for 6 years, and resigned of his own free will. Then the patient periodically worked at various enterprises of the city in simple working specialties. In recent years he had difficulty coping with work, was slow, inattentive, which was why he was fired. He did not serve in the army; he was commissioned by a neurologist (craniocerebral injury with craniotomy at the age of 8). He was married from 2002 to 2011 and was divorced at the initiative of the wife. He has a son (18 years old) and a daughter (16 years old) from marriage. He does not support communication with family now. The patient lives alone in a country house. He denies criminal record.

Medical History

The patient suffered a brain contusion at the age of 8. Subsequently, neurological pathology was not observed.

Suffering from a mental disorder since 2009. Then for no apparent reason, autochthonously (which indicates the endogenous genesis of a mental disorder) a depressive-paranoid state developed, which was stopped by taking the antidepressant paroxetine and the anxiolytic bromdihydrochlorophenylbenzodiazepine. Then,

throughout his life, he suffered several psychotic episodes of a paranoid structure. However, he did not turn to a psychiatrist for help. The spontaneous remissions were observed. During the illness, a steady and progressive decline in social functioning was noted: he gradually lost ties with his family, lost his home and job. A long-time interval from the manifestation of the disease to a steady decline in the social ladder indicates a moderate progression of the process. The reason for admission to a psychiatric hospital was delusional behavior against the background of a pronounced psychotic disorganization of thinking.

The mental status at the time of admission was characterized by the presence of acute sensual delusional ideas of a high position, persecution, relationship, damage, a querulative pattern of behavior, an unstable background of mood congruent to delusional experiences, pronounced delusional behavior, pronounced qualitative disorders of thinking in the form of diversity, paralogicality, semantic slippage, resonantism, anosognosia, which fit into the framework of the delusional variant of the paranoid syndrome.

The patient was diagnosed with paranoid schizophrenia, paroxysmal-progressive course. Paranoid syndrome (F20.016).

As part of inpatient treatment, the patient was prescribed haloperidol 15 mg/day, followed by dose titration to 20 mg/day. Against this background, the patient developed a resting tremor of medium amplitude in the right leg. For correction, the psychiatrist prescribed trihexyphenidyl 4 mg/day for 7 days. As part of the correction of the mental state, and taking into account the recorded poor tolerance of a typical AP - haloperidol, AP was changed by paliperidone 3 mg/day, followed by dose titration to 6 mg/day. Resting tremor did not stop. It was decided to resume taking trihexyphenidyl 4 mg/day. While taking the corrector, the tremor stopped slightly, but still bothered the patient. It was decided to switch the patient to quetiapine prolong 100 mg/day, followed by dose titration to 300 mg/day. Despite taking trihexyphenidyl, the patient was disturbed by severe tremor in the right leg.

The attending physician scheduled an initial consultation with a neurologist. It was diagnosed tardive dyskinesia, and prescribed biperiden at a dose of 4 mg/day.

While taking biperiden, no positive dynamics was noted. Then the patient was examined by a neurologist by V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology in the framework of studies of the effectiveness and safety of taking APs.

Neurological Examination 1 by Authors

The patient was diagnosed with mild postural tremor of the tongue, oromandibular dyskinesia of moderate severity in the form of low-amplitude movements of the lower jaw to the right and left and moderate chewing movements at rest. The lower jaw was shackled. Moderate facial hypomia was noted. There was a pronounced rest tremor in the right leg. In the prone position, a slight resting tremor in the left leg was also noted. In the upper and lower extremities, the extrapyramidal tone was increased, pronounced rigidity was noted. The patient performed a heel-knee test with bilateral misses due to tremor in the legs. The gait was hypokinetic. Moderate bradykinesia was noted. Thus, the patient showed symptoms of antipsychotic-induced parkinsonism, a mixed form, of a severe degree (grade 2.0 by the Hoehn and Yar scale) and mild oromandibular dyskinesia.

The neurologist recommended the appointment of amantadine 100 mg/day, followed by dose titration to 200 mg/day. After 2 months, a second visit by a neurologist was carried out as part of the study.

Neurological Examination 2 by Authors after 2 Months (after Prescribing Corrective Drugs)

Compared with the previous visit, oromandibular dyskinesia was stopped. The severity of the rest tremor in the right leg regressed to a moderate degree, and the tremor in the left leg was stopped. The patient was not disturbed by the presence of tremor. The

neurologist diagnosed antipsychotic-induced parkinsonism, mixed form, of moderate severity (grade 2.0 by the Hoehn and Yar scale). It was recommended to continue taking amantadine at a dose of 200 mg / day.

Conducted Therapy

- During the period of inpatient treatment, the patient was treated with the following drugs:
- Sol. Haloperidol 0.5% - 2.0 ml in muscle 2 times per day 5 days;
- Sol. Bromdihydrochlorhpenylbenzodiazipini 0.1% - 4.0 ml 2 times per day №10 days;
- Tab. Chlorpromazine 0.005 g per day, followed by an increase in dose to 0.02 g per day;
- Tab. Haloperidol 0.015 g, followed by an increase in dose to 0.02 g per day;
- Tab. Trigexifenidil 0.002 g, followed by an increase in dose to 0.004 g per day № 8;
- Tab. Paliperidone 0.003 g, followed by an increase in dose to 0.006 g per day;
- Tab. Ethylmethylhydroxypyridine succinate 0,375 g per day №30;
- Sol. Remaxol 400 ml intravenous drip №7;
- Sol. Glucose 5% 25 ml + Sol. Cytoflavin 10 ml intravenous drip №5;
- Tab. Quetiapine prolong 0.1 g, followed by an increase in dose to 0.3 g per day;
- Tab. Biperiden 4 mg/day;
- Sol. Amantadine 500 ml intravenous drip №5;
- Tab. Amantadine 0.2 g.

Pharmacogenetic Testing

PGx was carried out with the detection of carriage of polymorphic allelic variants and genotypes rs1800497 (NG_012976.1:g.17316G>A) of the *DRD2* gene.

Table 1. Pharmacogenetic testing data.

Gene OMIM	Chromosomal location	SNV / polymorphism	Genotype	Evaluation of the result
DRD2 (126450)	11q23.2	rs1800497 (g.17316G>A)	G/G	Homozygous genotype for the major allele G, low risk of developing antipsychotic-induced extrapyramidal disorders

Discussion

SNV rs1800497 of the *DRD2* gene is a candidate risk biomarker for the development of AIP and AITD. Despite this, according to studies by Bakker PR., Arbouw ME, Zhang JP. negative results were found, which were confirmed by the results of our observation [6-8]. These results can be explained by the fact that the SNV rs1800497 of the *DRD2* gene is located in the kinase gene closed as ankyrin and the kinase domain, base 1 (ANKK1), which is downstream the *DRD2* gene. Therefore, it is unlikely that this SNV occurred due to a change in the activity of the *DRD2* gene. According to McGuire V. [9], a high increase in the SNV rs1800497 of the *DRD2* gene was noted with the risk of developing Parkinson's disease in Caucasians (1.5-fold increased risk), while in Africans-Americans this risk fell ill by 80–90% ($p = 0.01$). The pathogenesis of AIP and Parkinson's disease is similar, which complicates the differential diagnosis. It is known that the patient has heredity on the father's side in the form of the presence of Parkinson's disease, which requires additional diagnostics for hereditary forms of Parkinson's disease. Of course, it cannot draw conclusions from one genetic biomarker. To identify the causes of the development of extrapyramidal syndrome in this patient, it

is necessary to do PGx using a complete genetic risk panel for developing AIP, AITD, and Parkinson's disease. This will help to understand the root cause of the development of this symptomatology.

Conclusions

The study of genetic predictors of AIP and AITD is not given due attention in neurological practice, and their frequency of occurrence is currently insufficiently studied in many regions of the world. Late diagnosis of AIP and AITD in patients with schizophrenia spectrum disorders does not allow for timely treatment at the early stages of the development of this neurological ADRs of AP therapy, which leads to a decrease or rapid disability, deterioration in the quality of life of patients.

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