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THE POSSIBLE ASSOCIATION OF POLYMORPHISM CYP2D6*4 WITH FREQUENT HOSPITAL STAYS OF PATIENTS WITH SCHIZOPHRENIA

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Abstract

The objective of the study was to investigate the genetic features that affect the metabolic rate of antipsychotics in patients with schizophrenia being frequently (at least once a year) treated in -hospital. The focus of the study was the genetic polymorphism CYP2D6*4 (1846G> A, rs3892097). A significant correlation between the presence of the CYP2D6*4 genetic polymorphism and frequent hospital stays of patients with schizophrenia was found. One of the probable reasons for this correlation may be a poor efficiency of drug therapy due to the slow metabolism of antipsychotics, most of which are the substrates for the CYP2D6 isoenzyme of cytochrome P450.

Key words: schizophrenia, frequent hospital stay, genetic polymorphism CYP2D6*4

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Introduction

Schizophrenia is one of the most severe, socially sensitive and disabling mental illnesses, mainly affecting young people. Patients with schizophrenia account for about 40% of the total number of patients being admitted to psychiatric hospitals and 70% of all those being admitted to hospital with psychosis [1]. About 90% of the budget allocated nationally for treatment of schizophrenia is spent by in-hospital patients due to their frequent hospitalization and the long periods of their treatment [2]. Also, the number of people being hospitalized frequently (at least once a year), is a minor fraction of the total number of hospital patients (about 10%), but their treatment costs the institution 10 times more and absorbs about 1/3 of the hospital budget allocated for treatment of all patients with schizophrenia [3].

The problem of frequent hospitalizations of patients with schizophrenia has been thoroughly studied, both from clinical and socio-psychological points of view. Two theories of frequent hospitalization exist. A clinical hypothesis explains the frequent hospitalizations by frequent relapses of the disease. A group of frequently hospitalized patients is characterized by an early onset of schizophrenia, a rapidly progressive course of the disease, protracted and treatment--resistant relapses, rapidly developing deficiency syndrome, and the presence of catatonic symptoms. This approach is based on the assumption that frequent hospitalization relates to biological prerequisites for the unfavourable course of schizophrenia and the resistance of these patients to treatment [4]. The behavioural hypothesis ("labelling theory") of frequent hospitalizations of patients with schizophrenia suggests that, regardless of the severity of psychopathological symptoms, the key factor that causes frequent hospitalization is the patient's psychological vulnerability and the extent of social tolerance toward him [5]. The idea of this approach is that the more the patient feels fear, insecurity, a sense of danger, shame and anger, the higher the risk of the next hospitalization [6]. Other risk factors include substance abuse [7, 8] and prior compulsory treatment [9].

Interestingly, the attempts to artificially reduce the duration of hospitalizations (the so-called-idea of de-institutionalization of psychiatry) inevitably leads to the increase in number and frequency of hospitalizations in the future. [10].

The hypothesis of this research is that this group of patients has some genetic features that affect the metabolic rate of antipsychotics, which is why the standard therapy is ineffective. The subject of the study was the polymorphism CYP2D6*4 of the gene encoding CYP2D6 isoenzyme of cytochrome P450. This gene is located at the 22nd chromosome, in locus 22q13.1 and is the most polymorphic, with more than 150 polymorphic loci described to date. The polymorphism CYP2D6*4 caused by the replacement of guanine (G) for adenine (A) at position 1846 (1846G> A) has the identification number rs3892097 [11].

Interest in this polymorphic locus originated from the increasing amount of data accumulated in recent publications

regarding its prevalence in the population, the determination of the type of metabolism and the correlation with the effectiveness of antipsychotic treatment of patients with schizophrenia.

The CYP2D6 isoenzyme accounts for 2 to 4% of the total number of cytochrome P450 isoenzymes and is involved in metabolism of about 25% of all currently known drugs, including antipsychotics [12].

Depending on the rate of the metabolism of drugs, the following phenotypes of people were suggested to exist in the human population: "slow" metabolizers, "intermediate", "fast (normal, or the most typical)", and "ultrafast" metabolizers. In the European population, the ratio of the expected (based on the genotype) frequencies of phenotypes in the allelic state of the CYP2D6 gene is as follows: "slow" metabolizers – 5%, "intermediate metabolizers" – 5%, "fast (normal / common)" – 88%, "ultrafast" metabolizers – 2% [13].

Evidence of a correlation between CYP2D6 polymorphisms and extrapyramidal side effects of antipsychotic therapy exists. In patients with a "slow" CYP2D6 genotype, an increased incidence of hypersedation was found [14].

However, the existing data on the relationship between CYP2D6 polymorphisms and clinical outcomes of schizophrenia (for which one of the markers is the rate of hospitalization) is insufficient. In existing publications, the direct data on the relationship between the frequency of hospitalizations with the presence of CYP2D6*4 polymorphism was only found once. The authors have found that the metabolic activity of CYP2D6 correlated independently of the DRD2 Taq1A polymorphism with the length of hospital stay in patients with schizophrenia [15]. This suggests that the subpopulation of patients with schizophrenia with uncommon CYP2D6 activity ("slow" metabolizers and "ultrafast" metabolizers) requires special attention of clinicians when prescribing antipsychotic treatment.

The objective of the study was to find a possible relationship between the frequency of hospitalizations of patients with schizophrenia and genetic factors of the "slow" type of metabolism of antipsychotics.

The plan was to formulate the genetic factors responsible for the slow metabolism of antipsychotics, being based on the available publication data, in groups of patients with schizophrenia with fundamentally different frequency of hospitalizations.

For the analysis, the CYP2D6 gene with allelic polymorphism determining the slow metabolism of antipsychotics was selected from the Pharmacogenomics Knowledge Base (PharmGKB), characterized by the population prevalence of about 20%, which allows our conclusions regarding schizophrenia in general to be extrapolated, the studied sample population consisting of 433 patients with schizophrenia. Data on the population prevalence of polymorphic loci were taken from the Allele Frequency Database (ALFRED). The prevalence of the polymorphic locus CYP2D6*4 (1846G> A, rs3892097) in Europe is 17.2%, in Russia – 20.0% [16]. The presence of this polymorphism is related to slow metabolism of any CYP2D6 substrates, including antipsychotics [17].

Materials and methods

The study was designed as cross-sectional and comparative; case-control methodology: the study group and the comparative group were represented by patients with schizophrenia differing in the frequency of hospitalizations.

The correlation between quantitative variables was studied in the entire group of studied patients. Test subjects were selected from people suffering from schizophrenia and stratified by the factor of hospitalization rate. At the time of the study, all participants were getting treatment at a psychiatric hospital. The study was approved by the healthcare ethics committee, and all patients gave informed consent to participate in it.

The general criteria for the inclusion of patients in the study were: the proven diagnosis of schizophrenia (in accordance with the diagnostic criteria of ICD-10); the duration of the disease (from the moment of the initial manifestation of psychotic symptoms) of a minimum of 10 years; and the age of 30 to 59 years.

The criteria for excluding patients from the sample study were: the presence of concomitant somatic diseases in the stage of decompensation; the presence of neurological disorders, including noticeable extrapyramidal symptoms at the time of the examination; comorbidity with other mental illnesses (including mental retardation, dementia, etc.); or forced hospitalization by court or in connection with systematic aggressive behaviour.

Data on the frequency of hospitalizations of patients were obtained from hospital records. To assess the frequency of hospitalizations, the hospitalization rate factor (HRF) was used, calculated as the number of hospitalizations in a psychiatric hospital for the entire duration of the illness divided by the duration (number of years) of the disease (starting from the moment of the initial manifestation of psychotic symptoms). The factor below one indicated that, on average, the patient was admitted to the hospital less often than once a year (HRF<1). This factor being one or more means that the patient was hospitalized on the average more often than once a year, which made it possible to classify him as a frequently hospitalized patient (HRF≥1).

The scale for the assessment of negative symptoms (SANS, the Scale for the Assessment of Negative Symptoms) [18] and the scale for the assessment of positive symptoms (SAPS, the Scale for the Assessment of Positive Symptoms) [19] were used to quantitatively assess the profile of the disease symptoms.

For molecular genetic studies, biomaterials (buccal epithelium) were taken from all patients included in the study, followed by DNA extraction using the standard phenol-chloroform extraction method; equalization of DNA concentration using NanoDrop 8000 (ThermoScientific, USA); Polymerase chain reaction (PCR) using MJ Mini and C1000

ThermalCycler (Bio-Rad, USA) followed by Restriction fragment length polymorphism (RFLP) analysis using specific endonuclease MvaI (Fermentas, Latvia) and genotyping using GelDocXR+ (Bio-Rad, USA).

For statistical processing of clinical data, the Statistical Package for the Social Science (SPSS'20) software was used. The WinPepi computer program was used for statistical processing of the distribution of genetic factors. The chi-square statistic analysis was used to assess the nature of the distribution of genetic factors. The obtained statistical data was estimated by calculating the significance level p.

The average age of the patients was 48.,9 ± 10.,3 years (38 to 59 years). The average age of the onset of the disease was 27,7 ± 8,.4 years (14 to 51 years), the average duration of the disease was 21.,4 ± 8.,6 years (12 to 50 years). Patients were admitted to a hospital from 4 to 57 times, with the average of 17.,3 ± 11.,1 times. The hospitalization rate ranged from 0.,13 to 3.,4 and averaged 0.,89 ± 0.,63. The number of patients in the group of frequently hospitalized patients (HRF≥1) was 212. The comparison group (HRF<1) consisted of 221 patients. The groups were comparable by gender (the fraction of males in the groups, $\chi^2\pm = 2,.43$, p>0.,05) and age (p>0.,05).

Results

Assessment of clinical symptoms

The clinical symptoms for patients with schizophrenia in a group of interest and a reference group were evaluated (Table 1).

Clinically, patients in the group with frequent hospitalizations (HRF≥1) had more pronounced negative symptoms in virtually all clusters of the SANS assessment. Differences between the groups were statistically significant.

Genotyping results

The analysis based on a comparison of the occurrence of polymorphism CYP2D6*4 among the patients with schizophrenia in the groups with HRF<1 and HRF ≥1 was carried out (Table 2).

The observed and expected occurrences of genotypes in the compared groups were not significantly different;, therefore, it can be stated that the distribution of genotype occurrences in the compared groups corresponds to the Hardy – Weinberg equation.

The occurrence of the "wild"¸ allele 1846G did not differ in the compared groups, while the of the mutant allele 1846A was significantly higher in the group of patients with frequent hospitalizations (Table 3).

The compared groups were completely different in the occurence distribution of all three genotypes (Table 4). Genotype 1846GG was significantly more frequently found in the group of seldom hospitalized patients ($\chi^2 = 4.,76$; p = 0.,029). Genotype 1846AA was found to be very rare, but nearly all patients with this genotype were often hospitalized ($\chi^2 = 5.,07$; p = 0.,024). The 1846GA heterozygous genotype was significantly more frequently observed in patients with frequent hospitalizations ($\chi^2 = 12.,00$; p = 0.,001), which clearly indicates the actual expansion of the 1846A, the minor allele, in schizophrenic patients with frequent hospitalizations.

Conclusions

Thus, we have identified a significant correlation between the presence of CYP2D6*4 polymorphism and hospitalization frequency, the latter being an important indicator for the characterization of patients with schizophrenia. Namely, it gets is obvious that the presence of the CYP2D6*4 polymorphism results in more frequent hospitalizations of patients with schizophrenia.

It is known that the occurrence of the CYP2D6*4 polymorphism does not differ among patients with schizophrenia and mentally healthy people [20]. Therefore, the data obtained regarding the distribution of occurrences of the CYP2D6*4 polymorphism may be used to assess risk of recurrent course of schizophrenia, but not the risk of predisposition to this disorder. What do the obtained results mean?

It is known that the CYP2D6*4 polymorphism is a non-functional one, leading to inactivation of the cytochrome P450 isoenzyme CYP2D6. Carriers of the polymorphism CYP2D6*4 are so- called "slow"¸ metabolizers, i.e. the individuals with a low metabolic rate of drugs, this low rate being related to a slowdown/deactivation of the functional activity of the cytochrome P450 isoenzyme CYP2D6. In "slow"¸ metabolizers, synthesis of the metabolic enzyme is absent, or the synthesis of a defective enzyme occurs, which leads to a decrease or complete inactivation of its enzymatic activity, and resultingly, in an accumulation of the drug in the body at high or even toxic concentrations [21]. Therefore, one of the probable reasons for the statistically significant relationship between the occurrence of polymorphism CYP2D6*4 with the high frequency of hospitalizations may be the low efficiency of drug therapy due to the slow metabolism of antipsychotics, most of which are substrates of the cytochrome P450 isoenzyme CYP2D6.

The results obtained are consistent with the existing publishedcation data on that the clinical form of schizophrenia, in which negative symptoms dominate, it is likely to result in a more severe outcome and a longer hospital stay [22]. Our results suggest that the polymorphism CYP2D6*4 is a factor of the genetic predisposition to a more severe course of schizophrenia with predominantly negative symptoms.

It might be possible that influence of the CYP2D6*4 polymorphism on a hospitalization rate is an indirect one. To date, one of the most important risk factors for frequent hospitalization is considered to be a low compliance of the patient with a supporting drug therapy schedule prescribed [23], which, in turn, may be due to a higher occurrence rate of side effects of antipsychotic therapy in carriers of this polymorphism.

The above stated correlation between the polymorphism CYP2D6*4 and the frequency of hospitalizations cannot be immediately explained, notwithstanding that several versions were put forward by the authors when analyszing the data obtained. Further research is also required before the results can be put into practice.

In this study, we assumed the all patients in the compared groups were getting the same treatment (drug therapy), in accordance with the Diagnostic and Treatment Protocol. Meanwhile, the ratio of typical to atypical antipsychotics could be different, which could affect the rate of hospitalization and the accuracy of results [24].

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