Rafał Świechowski

UM79/SSD/2015

Polimorfizmy i ekspresja wybranych cytochromów u pacjentów z depresją

Polymorphisms and expression of selected cytochromes in patients with depression

Rozprawa na stopień doktora nauk farmaceutycznych

Zakład Biochemii Farmaceutycznej i Diagnostyki Molekularnej

Uniwersytetu Medycznego w Łodzi

Promotor: prof. dr hab. n. farm. Ewa Balcerczak

Promotor pomocniczy: dr n. farm. Agnieszka Jeleń

Łódź 2019

Summary

Over 264 million people suffer from depression worldwide. It is the most common mental disorder that affects more women than men. The symptoms of depression include: depressed mood, anhedonia, lack of energy, sleep disorders and changes in appetite. Unfortunately, not all people who experience the mentioned symptoms report their problem to a physician. According to statistics, about 60% of patients do not seek help from a psychiatrist. The etiology of depressive disorders is still not fully understood. The most likely models of disease development are monoamine theory, related to disturbance of neurotransmission in central nervous system, and inflammatory model. There is an increased concentration of enzymes responsible for generating reactive oxygen species in patients with depression. A large percentage of patients achieve a weak therapeutic effect, and 20% of them have symptoms of the disease even two years after the diagnosis. The reason of weak treatment effectivness may be the clinical subtype of depression called Treatment-resistant depression. A branch of science called phamarcogenetics is looking for reasons for this phenomenon.

Cytochromes P450 is a group of enzymatic proteins involved in many reactions in body. One of their functions is the metabolism of xenobiotics introduced into our body, including drugs, toxins and carcinogens. Polymorphisms of genes encoding cytochromes may lead to the formation of a structurally altered protein that can show reduced or increased activity. Changes in protein activity have a significant impact on the metabolism of the used drugs, but may also play a significant role in the pathogenesis of some diseases, including depressive disorders.

The aim of the study was to assess the expression of the CYP3A4 gene in patients with depression and to assess the incidence of allelic variants: CYP3A4*1B, CYP3A5*3 and CYP2C19*2 in the study group compared to the control group.

Material for the study consisted of 108 DNA and 38 RNA samples isolated from peripheral blood leukocytes from patients suffering from recurrent depressive disorders (ICD-10 F33.0-F33.8) and 93 DNA samples derived from healthy individuals.

Real-time PCR was used to assess CYP3A4 gene expression in a group of patients with depressive disorders. The RFLP method was used to assess the incidence

98 of individual genotypes of CYP3A4*1B, CYP3A5*3 and CYP2C19*2 polymorphisms in the study and control groups.

In the healthy group, an increased frequency of the wild CYP3A5*1 allele was observed compared to the group of patients with depression. In the group of patients suffering from depression, the genotype *1/*3 (11.4%) was more often identified compared to the control group (1.1%). A statistically significant correlation between the incidence of individual genotypes and alleles of the CYP3A5*3 polymorphism and age at diagnosis was demonstrated Patients with the genotype *3/*3 were diagnosed at a younger age, on average 7 years earlier than patients with the genotype *1/*3. A statistically significant relationship between the presence of the CYP2C19*2 allele and the efficacy of the treatment was demonstrated. Patients with at least one CYP2C19*2 allele achieved statistically better results compared to patients who did not have this allele. The relative level of CYP3A4 expression in patients with depressive disorders was differentiated. Statistical analysis did not show any significant correlation between the relative level of CYP3A4 expression and the examined clinical features.

The results presented in the paper show a possible protective role of the CYP3A5*3/*3 genotype in the development of depressive disorders. On the other hand, the CYP3A5*3/*3 genotype may be responsible for the occurence of first symptoms of disease at younger age. The results also show the potential impact of the CYP2C19*2 allele on better outcomes. Changes in the relative level of the CYP3A4 gene expression do not have a significant impact on the development, course of disease and efficacy of depression treatment.