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Features of the COPD course in patients with different alleles of C79G (rs1072714) of ADRB2 gene

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Chronic obstructive pulmonary disease (COPD) is a widely spread disease, that can be prevented and treated. As it was mentioned in the GOLD guidelines, genetic factors have a prominent impact on the development of COPD. A great amount of different genes is involved into the development of COPD. They influence processes of inflammation, fibrosis and regulation of airways reactivity. Polymorphism of ADRB2 gene is of a particular interest as it is associated with the development of COPD and response to beta-2 agonists, which are the main drugs used in the treatment of COPD. The aim of our study was to investigate an impact of the polymorphism of ADRB2 gene on the clinical course of COPD. We collected source data, medical history in all patients in order to assess smoking status and smoking experience, clinical group of COPD according to GOLD classification, total amount of exacerbations, exacerbations treated in in-patient and out-patient conditions, data about use of antibiotics, glucocorticosteroids and methylxanthines. Blood was collected in all patients for the genetic analysis of ADRB2 gene polymorphism. Among COPD patients 65 (65 %) had changes in ADRB2 gene. 26 patients (26 %) had mutation and 39 patients (39 %) had polymorphism of ADRB2 gene, which indicate possible relation of ADRB2 gene with the COPD development. Patients of group 1, C79C allele carriers, had milder COPD course, which presented with the significant difference in the of GOLD D patients in this group (17.14 ± 7.13 %) and group 2, C79G allele carriers, (58.97 ± 8.15 %) and group 3, G79G allele carriers, (34.61 ± 9.59 %). Group 1 patients had lower amount of exacerbations (2.543 ± 0.281) when compared to group 3 (2.963 ± 0.273), and lower amount of hospital admissions (1.031 ± 0.154) when compared to group 2 (1.332 ± 0.167). Group 1 patients also used less antibiotics then other groups. So, ADRB2 gene polymorphism in C79G positions is a prognostic factor of the severity of COPD course. It is associated with the greater amount of exacerbations and hospitalizations and also greater antibiotic use.

Keywords: COPD, ADRB2, polymorphism, clinical course, exacerbation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a widely spread disease, that can be prevented and treated. It is characterized by the persistent symptoms and a decrease in pulmonary function due to the pathological changes in airways and/or alveoli, that a provoked by the significant impact of harmful particles in the susceptible organism [14]. According to the Burden of Obstructive Lung Disease study 10.1 % of the population have COPD (11.8 % men; 8.5 % women). Incidence of COPD is also high in never-smokers (3-11 %) [4, 10]. COPD is a cause of death in 3 million cases each year [1]. According to different predictions COPD might be a cause of death in 5.4 million cases by the year 2060 due to the wider spread of smoking

in the developing countries and ageing of population in the developed countries [12].

As it is mentioned in GOLD guidelines, intrinsic or genetic factors play an important role in the COPD development along with the extrinsic factors, such as smoking [2]. According to the data from different studies a great amount of genes is involved in the development of COPD. These genes impact processes of inflammation, fibrosis and airways reactivity [15]. One of such genes, that is associated with the development [17] and severity of COPD [8], and also response to beta-2 agonists is ADRB2 [5, 16].

Different studies have demonstrated a difference in

response to beta-2 agonists and inhaled corticosteroids depending on the ADRB2 polymorphism [7, 9], that can directly impact a clinical course of COPD [3].

So the aim of our study was to investigate a prevalence of polymorphic alleles of ADRB2 gene among COPD patients, correlation with the development of COPD and its clinical course.

Materials and methods

The study was carried out at the department of propaedeutic of internal medicine of Vinnytsia National Pirogov Memorial Medical University and Communal Non-profit enterprise "Vinnytsia City Clinical Hospital № 1". Approval of Local Ethics Committee was obtained prior to the study start. All participants signed an informed consent form prior to the inclusion into the study.

100 patients with the diagnosis of COPD were included into the study. Their average age was 64.09 ± 1.94 years. 66 were men (66 %) and 34 women (34 %).

68 patients (68 %) were smokers with the average smoking experience of, 24.44 ± 4.84 pack-years. Average COPD duration was 9.351 ± 2.423 years.

Exclusion criteria were the following: any clinically significant disease, laboratory disorder or other information in the medical history or during physical examination, that can influence patient's safety in the study, inability of the patient to follow study procedures, abuse of alcohol or drugs at the moment of investigation or in the medical history.

At the baseline visit we collected source documentation, medical history for the assessment of smoking status and smoking experience, clinical group of COPD, total amount of exacerbation, amount of exacerbations treated in in-patient and out-patient condition, information regarding the use of antibiotics, glucocorticosteroids and

methylxanthines.

Blood samples for the genetic analysis of ADRB2 gene polymorphism were collected in all patients. According to the obtained data all patients were divided into 3 groups: group 1 (C79C allele carriers) - 35 patients (35 %), group 2 (C79G allele carriers) - 39 patients (39 %), group 3 (G79G allele carriers) - 26 patients (26 %).

Statistical analysis was performed using SPSS statistical program (Version 17.0 for Windows; USA).

Results

Group 3 patients, G79G allele carriers, were older than group 1 patient, C79C allele carriers ($p < 0.05$). Study groups did not differ by the gender content. There was a tendency towards a smaller part of smokers in group 3 when compared to group 1 ($p = 0.075$) and group 2 ($p = 0.061$); tendency towards smaller smoking experience in group 3 when compared to group 2 ($p = 0.063$); and tendency towards longer duration of COPD in group 3 when compared to group 1 ($p = 0.067$) and group 2 ($p = 0.054$) (Table 1).

Table 2 represents parts of the patients with different COPD clinical groups according to the GOLD classification in different study groups.

There was no statistically significant difference between part of GOLD B patients in the studied groups. A smallest part of GOLD C patients was observed in group 2 patients, C79G allele carriers, when compared to group 1 and 3 ($p < 0.05$). There was smaller part of GOLD D patients in group 1 when compared to group 2 ($p < 0.01$) and group 3 ($p < 0.05$) (Table 2). So, we can assume, that C79G and G79G allele carriage is associated with the more severe COPD course.

A number of exacerbations in a year prior to the study in group 1 was: (2.543 ± 0.281) , such that required

Table 1. Content of study groups by age, gender, smokers, smoking experience and COPD duration.

Values	Group 1	Group 2	Group 3	P_{1-2}	P_{1-3}	P_{2-3}
Age	61.57 ± 2.58	64.17 ± 2.10	66.96 ± 2.41	>0.05	<0.05	>0.05
Men, %	60.00 ± 8.07	74.35 ± 7.33	61.53 ± 9.03	>0.05	>0.05	>0.05
Women, %	40.00 ± 8.07	25.64 ± 7.33	38.46 ± 9.03	>0.05	>0.05	>0.05
Smokers, %	68.57 ± 8.19	71.79 ± 7.78	61.53 ± 9.03	>0.05	$=0.075$	$=0.061$
Smoking experience, pack-years	23.60 ± 5.52	27.58 ± 4.58	20.84 ± 5.34	>0.05	>0.05	$=0.063$
COPD duration, years	8.113 ± 1.825	8.074 ± 1.207	11.52 ± 2.02	>0.05	$=0.067$	$=0.054$

Notes: here and in the next table, p_{1-2} - significance between group 1 and 2 values; p_{1-3} - significance between group 1 and 3 values; p_{2-3} - significance between group 2 and 3 values.

Table 2. Part of the patients with different COPD clinical groups in study groups (%).

Values	Group 1	Group 2	Group 3	P_{1-2}	P_{1-3}	P_{2-3}
GOLD B	9 people 25.71 ± 8.23	7 people 17.94 ± 6.60	4 people 15.38 ± 7.86	>0.05	>0.05	>0.05
GOLD C	20 people 57.14 ± 8.24	9 people 23.07 ± 6.83	13 people 50.00 ± 10.59	<0.05	>0.05	<0.05
GOLD D	6 people 17.14 ± 7.13	23 people 58.97 ± 8.12	9 people 34.61 ± 9.59	<0.01	<0.05	>0.05

Fig. 1. A number of exacerbations in the year before the investigations in study groups.

Fig. 2. A part of patients, that required treatment with antibiotics, GCS and methylxanthines in study groups in a year prior to the study.

Fig. 3. An average amount of antibiotic, GCS, methylxanthines courses in study groups in a year prior to the study.

hospitalization - (1.031 ± 0.154), such that were treated in out-patient settings - (1.507 ± 0.214). A number of exacerbations in group 2 was: (2.744 ± 0.237), such that required hospitalization - (1.332 ± 0.167), such that were treated in out-patient settings - (1.428 ± 0.186). A number of exacerbations in group 3 was: (2.963 ± 0.273), such that required hospitalization - (1.272 ± 0.134), such that were

treated in out-patient settings - (1.692 ± 0.118).

There was a statistically significant difference between the number of total exacerbations in group 1 and 3 ($p < 0.05$), and number of hospitalizations between group 1 and 2 ($p < 0.05$) (Fig. 1). So, we can assume, that G79 allele carriage is associated with the greater amount of exacerbation in patients with COPD.

In a year before the study a number of patients that required antibiotics in group 1 were 29 patients (82.85 ± 7.13 %), in group 2 - 39 (100.0 %), in group 3 - 24 patients (92.30 ± 5.97 %).

Number of patients that required treatment with glucocorticosteroids (GCS) in group 1 was 16 patients (45.71 ± 8.36 %), in group 2 - 25 patients (64.10 ± 8.77 %), in group 3 - 14 patients (53.84 ± 10.53 %).

Number of patients that required treatment with methylxanthines in group 1 was 14 patients (40.00 ± 8.073 %), in group 2 - 18 patients (43.58 ± 8.28 %), in group 3 - 8 patients (30.76 ± 9.01 %).

A bigger part of group 2 patients required antibiotics when compared to two other groups ($p < 0.05$). There was a tendency towards a higher used of antibiotics in group 3 when compared to group 1 ($p = 0.061$). Group 2 patients used GCS more often when compared to group 1 patients 1 ($p < 0.05$). There was no significant difference in the use of methylxanthines in the study groups (Fig. 2). So, we can assume, that C79G and G79G allele carriage is associated with the greater use of antibiotics during COPD exacerbations.

An average amount of antibiotic courses in group 1 was (1.372 ± 0.161) courses, in group 2 - (1.593 ± 0.138), in group 3 - (2.002 ± 0.226); an average amount of GCS courses in group 1 was (0.891 ± 0.243) courses, in group 2 - (1.307 ± 0.321), in group 3 - (0.726 ± 0.164); an average amount of methylxanthines courses in group 1 was (0.616 ± 0.176) courses, in group 2 - (1.198 ± 0.344), in group 3 - (0.416 ± 0.138) (Fig. 3). Group 3 patients used antibiotics more often when compared to group 1 ($p < 0.05$) and group 2 ($p < 0.05$). Group 2 patients used GCS and methylxanthines more often when compared to two other groups ($p < 0.05$). So, we found, that patients with COPD and G79G allele have a greater amount of exacerbations and required greater use of antibiotics.

An average duration of treatment with antibiotics in group 1 was (10.89 ± 1.39) days, in group 2 - (12.15 ± 1.19) days, in group 3 - (14.26 ± 1.71) days. An average duration of treatment with GCS in group 1 was (3.627 ± 0.813) days, in group 2 (5.283 ± 1.054) days, in group 3 - (3.651 ± 0.776) days. An average duration of treatment with methylxanthines in group 1 was (3.449 ± 0.926) days, in group 2 - (4.231 ± 1.104) days, in group 3 - (2.234 ± 0.786) days.

Treatment with antibiotics was longer in group 3 when compared to group 1 ($p < 0.05$). There was a statistically significant difference between the duration of treatment with GCS in group 2 and other groups ($p < 0.05$). There was a statistically significant difference in the treatment duration

Fig. 4. An average duration of treatment with antibiotics, GCS and methylxanthines in study groups in a year prior to the study.

with methylxanthines in group 2 and group 3 ($p < 0.05$) (Fig. 4). So, we can think, that a G79G allele carriage is associated with the greater use of antibiotics.

Discussion

Data about impact of ADRB2 gene polymorphism on the development of COPD differ in different studies. Some part of the investigations indicates, that a part of polymorphic or mutant alleles of ADRB2 gene is greater in patients with COPD, than in the control group without COPD [6]. Some authors considered a relation between the ADRB2 gene polymorphism and COPD development [18] and earlier COPD manifestation [11]. In our study we demonstrated a big part of polymorphic and mutant alleles in patients with COPD, but the weak point of our study is an absence of the control group. Nonetheless our data corresponds with the data of other Ukrainian authors [5], so we can state the presence of the relation between the ADRB2 gene polymorphism and development of COPD. Also COPD course was longer in patients with the mutant allele of ADRB2 gene, when compared to the group with the wild allele.

Data about impact of ADRB2 gene polymorphism on the clinical course and treatment efficacy in patients with COPD differs a lot. Rotterdam study indicates a relation between ADRB2 gene polymorphism and clinical course of COPD, particularly with exacerbations in patients, who are treated with long-acting beta-2 agonists [8]. Part of the investigations indicates a possible role of the ADRB2 gene polymorphism as a predictor of the response to beta-2 agonists in patients with COPD [13]. But data from a big meta-analysis reports no difference in the response to beta-2 agonists in multiple ethnic groups [8]. Data of our

investigations corresponds with the data from Rotterdam study, as we found a relation between the ADRB2 gene polymorphism and number of exacerbations in patients with COPD.

During the literature search we found no publications, that compared an influence of ADRB2 gene polymorphism on the use of main groups of drugs, that are used in the treatment of COPD exacerbations. So, further investigations are needed in order to study relation of ADRB2 gene polymorphism with different clinical parameters.

Conclusion

1. In general, 65 of patients (65 %) with COPD had changes in ADRB2 gene. 26 patients (26 %) had mutation (G79G) and 39 patients (39 %) had polymorphism of ADRB2 gene, that indicate a possible relation of this gene with COPD development.

2. Group 1 patients, C79C allele carriers, had milder course of COPD, which manifested in the significantly lower part of patients with GOLD D in this group (17.14 ± 7.13 %) and group, C79G allele carriers, (58.97 ± 8.15 %) and group 3, G79G allele carriers, (34.61 ± 9.59 %).

3. Group 1 patients had less exacerbations (2.543 ± 0.281) when compared to group 3 (2.963 ± 0.273) and less hospitalizations (1.031 ± 0.154) when compared to group 2 (1.332 ± 0.167). So, C79C allele carriage is associated with milder course of COPD.

4. Part of the patients that required treatment with antibiotics in group 1 (82.85 ± 7.13 %) when compared to group 2 (100.0 %). Similar pattern was observed for GCS (45.71 ± 8.36 % vs 64.10 ± 8.75 %). This group of patients used antibiotics rarer (1.372 ± 0.161 courses) when compared to group 2 (1.593 ± 0.138 courses) and group 3 (2.002 ± 0.226 courses); they also used less GCS (0.891 ± 0.243 vs 1.307 ± 0.321) and methylxanthines (0.616 ± 0.176 vs 1.198 ± 0.344) when compared to group 2.

5. Duration of treatment with antibiotics in group 1 (10.89 ± 1.39 days) was significantly lower than in group 3 (14.26 ± 1.71 days), duration of treatment with GCS in group 1 (3.627 ± 0.813) was lower when compared to group 2 (5.283 ± 1.054). So C79C allele carriage is associated with the milder course of COPD, smaller usage of antibiotics and methylxanthines.

6. Appearance of polymorphic (C79G) and mutant (G79G) alleles of ADRB2 gene was associated with the more severe course of COPD, higher number of exacerbations and hospital admissions, higher need in antibiotics and GCS, that indicates its important role in the regulation of the reactivity of airways and response to treatment.

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