Relationship Between Childhood Asthma and C3435T Multidrug Resistance 1 Gene

Çocukluk Astımı ve C3435T "Multidrug Resistance 1" Geni Arasındaki İlişki

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Özet

Amaç: Çocukluk astımı ve C3435T "multidrug resistance 1" gen polimorfizmi arasındaki ilişkiyi göstermek amaçlanmıştır. Gereç ve Yöntem: Astımlı 58 çocuk ve sağlıklı 54 çocuk çalışmaya katılmıştır. İstatistiksel analiz için kikare ve "Fisher's exact" testleri kullanılmıştır. Bulgular: "Multidrug resistance-1" geni için normal, heterozigot ve homozigot polimorfizm, astımlı çocukların sırasıyla 12 (%20,7), 31 (%53,4) ve 15 (%25,9)'inde bulunmuştur. Sağlıklı çocuklarda normal, heterozigot ve homozigot polimorfizm, sırasıyla 18 (%33,3), 28 (%51,9) ve 8 (%14,8)'inde bulunmuştur. "Multidrug resistance 1" geni açısından astımlı ve sağlıklı çocuklar arasında fark görülmemiştir. Homozigot polimorfizm ağır persistan grupta, orta ve hafif persistan gruba göre (p=0,001) ve kızlarda, erkeklere göre daha yüksek bulunmuştur (p=0,001). Tartışma: Farklılığın ağır persistan astımlı hastalardan kaynaklandığı söylenebilir. Bu bilgi, hastalar astım tanısı aldığında "multidrug resistance 1" genine bakarak klinisyenlerin hastaları sınıflandırmasına yardımcı olabilir. Böylece, özellikle kritik derecedeki hastaların tedavisi erken başlanabilir ve uzun dönemli takibi yapılabilir. Ayrıca özellikle kadın hastalar için cinsiyete özel tedavi planlanabilir.

Anahtar Kelimeler

Astım; Çocuklar; "Multidrug Resistance-1" Geni

Abstract

Aim: It was aimed to show the relationship between childhood asthma and C3435T multidrug resistance 1 gene polymorphism. Material and Method: Fifty eight children with asthma and 54 healthy children participated to the study. Chi-square and Fisher exact tests were used for statistical analysis. Results: Wild, heterozygous and homozygous polymorphism for multidrug resistance -1 gene were found respectively in 12 (20.7%), 31 (53.4%), and 15 (25.9%) of children with asthma. In healthy children, wild, heterozygous, and homozygous polymorphisms were found respectively in 18 (33.3%), 28 (51.9%), and 8 (14.8%) participants. There was no statistical difference between asthmatic and healthy children in terms of multidrug resistance 1 gene polymorphism. Homozygous polymorphism was found higher in severe persistent group than moderate and mild persistent groups (p=0.001) and in girls than boys (p=0.001). Discussion: It may be said that the difference was resulted from severe persistent asthmatic patients. And this information helps clinicians to rank the patients in terms of asthma by looking multidrug resistance 1 gene when the patient was diagnosed as asthma. Hence, treatment of patients, especially with crucial degree may begin earlier and its long-term pursuance can be made. In addition, gender-specific treatment can be planned especially for female patients.

Keywords

Asthma; Children; Multidrug Resistance-1 Gene

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Introduction

Asthma is a type of disease that cause inflammation chronically on the airway. It is the most common chronic disease that seen at children. There are some signs and symptoms such as cough, breathlessness, chest tightness and wheezing that seen in asthma [1]. It is not easy to know who will develop asthma in the future, but it is already known that environmental tobacco smoke and some factors on surrounding as well as genetic predisposition result in the development of asthma [2]. Asthma is a complex disease that shows genetic heterogeneity due to the interaction of several genes [2].

The prevalence of asthma is increasing worldwide and has been becoming a vital problem for public health. For this reason, the prevention of asthma is important [3]. Environmental factors can be arranged, however, genetic predisposition cannot be modified. So, having information about genetic factors may be important in order to provide early detection and prevention on the diseases. Out of this, it is suggested that few genetic factors have protective role for the lung. For example, multidrug resistance (MDR) 1 gene proteins may provide resistance against oxidative injury in the pulmonary tissue [4].

The multidrug resistance 1 (MDR1) gene is located on chromosome 7 at q21. It encodes a plasma membrane P-glycoprotein (P-gp) which consists of 1280 amino acids. P-glycoprotein functions as a pump molecule and reduces intensity of drugs by excreting them from the intracellular space [5]. It is a member of a large transport family which is known as the ATP-binding cassette (ABC) superfamily [6]. ATP-binding cassette transporters are basically found in all cells and play key roles in physiology. They transport drugs, lipids and steroids across membrane systems. ATP-binding cassette transporters also play important roles in the immunologic events and may lead to hereditary diseases [7]. P-glycoprotein is found in the apical surface of many cells with excretory functions include the liver, kidney, small intestine, stomach, and the blood–brain barrier [8]. Similar to many other tissues such as adrenal gland, liver, prostate, placenta, uterus; pulmonary tissue and trachea also show considerable amount of transcriptional activity for various ABC transporters [7]. In the pulmonary tissue, P-gp expression has been well studied for lung cancer [9]. It is suggested that these transporters are assigned to protect the pulmonary tissue against harmful substances [4].

Multidrug resistance gene 1 polymorphism was firstly defined by Hoffmeyer et al [10]. There are many single nucleotide polymorphism on MDR1 gene. The effect of this polymorphism on pulmonary disease is still controversial [11]. There is conclusive evidence showing that energy-dependent transporters have important functions in the pulmonary tissue. For example, it was suggested that, the main reason for the pathology of cystic fibrosis disease was the mutation on "Cystic fibrosis transmembrane conductance regulator" gene due to MDR1 polymorphism [12]. The best known single nucleotide polymorphisms on MDR1 gene are C3435T, C1236T, and G2677T/A [13]. Although there are a few studies about SNP C1236T and G2677T/A, many studies have been found related to C3435T polymorphism [14-16]. But, we did not find any study associated with C3435T SNP and childhood asthma. Single nucleotide polymorphism C3435T, located in exon 26 of the MDR-1 gene, results in decreased expression of P-gp [17]. Because asthma is an inflammatory disease, in current study evaluation of the relationship between childhood asthma and C3435T MDR1 gene polymorphism which plays a role in the inflammatory process was aimed. In addition, correlation of this gene polymorphism with the severity of asthma was also investigated.

Material and Method

One hundred and twelve children between the ages of 6 to 17 years were included in the study. The study group consists of 58 children with asthma and 54 healthy volunteers as control. The children with asthma not currently under treatment were included in the study. According to Global Initiative for Asthma (GINA) protocol, classification of asthma was made as mild persistent, moderate persistent and severe persistent asthma [18]. Participants with comorbid diseases such as chronic pulmonary disease, congenital heart disease, chronic renal failure, and growth retardation were excluded from the study. The study was conducted at the Cumhuriyet University hospital in between 2011-2012 years.

Polymorphism analysis: Three ml venous blood samples were taken into EDTA tubes from all participants. These blood samples were stored at -20°C until ready to work. Genomic DNA was extracted from 100 µl of whole blood using the Invitek kit (Invitek, Invisorb spin blood, Germany). Amplification of the multidrug resistance 1 gene was performed in a biotin labeled single multiplex amplification reaction and then 3435 CT polymorphism was evaluated. Polymerase chain reaction (PCR) was carried out in a Perkin Elmer Gene amp 9600 Thermal Cycler. The study protocol was performed as follows: 1) an initial melting step of 2 minutes at 94°C, 2) 35 cycles of 15 seconds at 94°C, 3) 30 seconds at 58°C 4) 30 seconds at 72°C, and 5) a last elongation step of 3 minutes at 72°C. The Strip Assay technique (Vienna Lab, PGX-HIV Strip Assay GmbH, Austria), based on the reverse-hybridization method, was used for polymorphism analysis.

Statistical analysis: The SPSS software package version 14 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. Data from the children with asthma and from the healthy children were analyzed by chi-square (x2). Comparison of study groups among each other analyzed by Fisher's exact test. $P < 0.05$ was considered as significant.

Ethical disclosures: The current study was approved by the ethics committee of Cumhuriyet University (Date: 13 December 2011 and decision number: 2011/028).

Right to privacy and informed consent: The children or their families signed an informed consent form in order to be able to participate to the study.

Results

The study group was composed of 31 boys (53.4 %) and 27 girls (46.6 %) while the control group was composed of 23 boys (42.6 %) and 31 girls (57.4 %). There was no statistical difference according to age, height and weight of patients and control groups.

Multidrug resistance 1 gene polymorphism

The comparison of multidrug resistance 1 CC (wild type), CT (heterozygous) and TT (homozygous) gene polymorphisms was

carried out between the children with asthma and healthy children. The results of the current study are shown in table I. According to these results, there was no significant statistical difference between the children with asthma and healthy children in terms of MDR-1 polymorphisms.

Table I. Distribution of MDR-1 genotype in patients with asthma and control group

Polymorphism type	Patients with asthma n (%)	Control group n (%)
Heterozygous (C/T) MDR1 polymorphism	31 (53.4)	28 (51.9)
Homozygous (T/T) MDR1 polymorphism	15 (25.9)	8 (14.8)
Wild type (C/C) MDR1 polymorphism	12 (20.7)	18 (33.3)
Total	58 (100)	54 (100)

p>0.05 MDR: multidrug resistance

Children with asthma were divided into three groups as mild persistent, moderate persistent and severe persistent asthma. This classification was made according to GINA protocol [18]. Mild persistent, moderate persistent and severe persistent asthmatic groups were composed of 24, 17 and 17 patients respectively. MDR1 CC (wild type), CT (heterozygous) and TT (homozygous) gene polymorphisms were compared among children with asthma, and homozygous TT polymorphism was found significantly higher in severe persistent asthmatic group than that of moderate and mild persistent groups (p=0.001). In moderate persistent group, heterozygous CT polymorphism was found significantly higher than that of mild persistent group (p=0.001). The results are shown in table II.

Table II. Distribution of MDR-1 genotype in patients with asthma

Polymorphism type	Mild persistent asthman (%)	Moderate persistent asthma n (%)	Severe persistent asthma n (%)
Heterozygous (C/T) MDR1 polymorphism	14 (58.4)	12 (70.6)†	5 (29.4)
Homozygous (T/T) MDR1 polymorphism	2 (8.3)	2 (11.8)	11 (64.7)¶
Wild type (C/C) MDR1 polymorphism	8 (33.3)	3 (17.6)	1 (5.9)
Total	24 (100)	17 (100)	17 (100)

†Heterozygous polymorphism was seen more in moderate persistent asthma than mild persistent asthma
¶Homozygous polymorphism was seen more in severe persistent asthma than mild and moderate persistent asthma
MDR: multidrug resistance

When the comparison at the study group was based on gender, homozygous TT polymorphism was found significantly higher than heterozygous CT and wild type CC polymorphism in girls, while in boys heterozygous CT polymorphism was found significantly higher than homozygous TT and wild type CC polymorphism (p=0.001). The results about gender and polymorphism type were shown in table III. However, in the control group there was no statistical difference between boys and girls in terms of genotype (p>0.05).

Allelic frequency

In healthy control; C and T allele frequencies were found as 59.3% and 40.7 % respectively; while in children with asthma; C and T allele frequencies were found as 47.4% and 52.6% respectively.

Table III. Distribution of MDR-1 genotype according to gender

Polymorphism type	Girls	Boys	p
Heterozygous (C/T) MDR-1 gene n (%)	11 (40.7)	20 (64.5)*	P=0.001
Homozygous (T/T) MDR-1 gene n (%)	13 (48.1) α	2 (6.5)	P=0.001
Wild type (C/C) MDR-1 gene n (%)	3 (11.1)	9 (29.0)	
Total n (%)	27 (100)	31 (100)	

*p= 0.001: heterozygous polymorphism was higher than homozygous and wild type polymorphism in boys
αp=0.001: homozygous polymorphism was higher than heterozygous and wild type polymorphism in girls
MDR: multidrug resistance

Discussion

Asthma is the most common chronic illness among children in many parts of the world. It is characterized by airway inflammation and narrowing of airway resulting in cough, wheezing, shortness of breath, fatigue. Asthmatic patients generally have impairment of their daily activities due to the lack of the disease control [18].

Early treatment is important for asthma, because a condition called remodeling occurs as the disease progresses. Risk of developing remodeling increases as the inflammation in asthma becomes chronic. Remodeling occurs both in large and in small airways. It is a heterogeneous event that cause structural changes in the airway, airway cells, and connective tissue as a result of migration, maturation and redifferentiation. Structural changes in the airway include epithelial damage, fibrosis in subepithelial area, prolonged repair process, excessive production of profibrotic growth factors, revascularization, and increase in smooth muscle mass [19]. As a result, remodeling leads to thickening and narrowing in the airways. These changes are irreversible and do not improve even with appropriate treatment [19]. Chronic damage due to remodeling can be avoided by early diagnosis and early treatment of asthma [19]. There is no cure for the disease completely, but in order to recover the symptoms, good treatment is available [1,2,19]. The aim of asthma treatment is to provide symptom control for a long period of time, prevent asthma attacks, decrease and control airway inflammation, and maintain good pulmonary function.

MDR1 gene polymorphism and asthma severity

ABC transporter family has been divided into seven subgroups extends from ABCA to ABCG. P glycoprotein is located in the subgroup of ABCB1. So far, in the human body, 48 ABC transporters have been identified in the seven subgroups. These transporter proteins are find almost in every cell and in all species and it is known that they all have basic physiological role in the cells [6]. In the pulmonary tissue, MDR1 gene and release of P-glycoprotein have been well studied especially in the lung cancer [9]. It is thought that, the existence of these transport proteins in the pulmonary tissue is important for the protection of this tissue from endogenous and exogenous toxigenic substances [9]. In addition, the efficiency of inhaled aerosol medications and of many drugs that are metabolized in the pulmonary tissue may be dependent on the presence of various energy transporters and on their activities [11]. Also many ABC transporter is required for the drugs to reach the activation site in the lung [11]. P glycoprotein is involved in cellular defense against environmental factors and they are released from the apical surface of liver and intestinal tissues. In the lung, P glyco-

protein is released from apical surface of ciliated epithelial cells or from apical and lateral surfaces of ciliated collecting ducts and from bronchial glands [20].

To our knowledge, the importance of multidrug resistance-1 gene polymorphisms had not been studied in children with asthma. This was the first study that demonstrated the association between C3435T MDR1 gene polymorphism and asthma in children. In current study, there was no significant difference in MDR1 gene polymorphism between children with asthma and healthy control group. However MDR1 TT homozygous mutation was significantly higher in children with severe persistent asthma than in children with moderate persistent and mild persistent asthma. Although it was observed that heterozygous mutation was diagnosed more in patients with moderate persistent asthmatic patients as compare to mild persistent asthmatic patients, homozygous mutation was diagnosed more in the severe persistent asthmatic patients. The situation which is important here is identifying especially severe persistent asthmatic patients and taking them into close follow-up. Severe persistent asthmatic patients are generally less than other asthmatic patients in number and covers 4.5% of childhood asthma [21]. But morbidity and mortality is seen more in these patients. It also causes absenteeism in schools among children more than other asthma groups. In addition severe asthma in childhood may be an indication of persistence of asthma later in adulthood. Decreased lung function occurs early in childhood and does not change at a later time with aging [1,2]. Observing homozygous mutation more in such patients as compare to other patients further increases the importance of this situation. Patients with whom homozygous mutation is diagnosed may be informed about heavy disease, importance of disease and necessity of regular treatment in addition to regular control. By doing so, having an attack or a possible attack in addition to chronic complications may be prevented by efficient treatment. Based on haplotype analysis, the C-C and C-T shift could be protective from severe asthma in children.

There have been variable studies about MDR1 gene polymorphism in different diseases. Taheri et al [14] studied a possible association be¬tween MDR1 gene C3435T polymorphism and its expression in 54 breast cancer patients. They did not see any difference in the frequency of C3435T polymorphism between patients and healthy controls. But, they found significant association between MDR1 expression levels and C3435T polymorphism in the patients. They reported that individuals who were homozygous for the T allele had a significantly decreased P glycoprotein expression level compared to those homozygous for the C allele [14]. They reported that, C3435T polymorphism may play a role in inducing drug resistance by altering the expression level of the MDR1 gene.

Akın et al [15] studied 31 childhood acute idiopathic thrombocytopenic purpura patients and they found no association in genotype and allele distribution between the patients and the control group. In addition, there was no difference in the treatment response between MDR1 gene genotypes.

In another study conducted on 41 adult patients, the T allele polymorphism of the MDR1 gene was shown to be associated with chronic obstructive pulmonary disease [4]. In one study, nephrotic syndrome children with mutations in MDR1 gene were found to be susceptible to steroid-resistant nephrotic syndrome [16]. In the study of Ozen et al [22] it was indicated that C3435T polymorphism MDR1 gene was associated with colchicine resistance in nonresponder familial Mediterranean fever patients. In addition, T allele frequency was found higher in these patients. Similar to these results, in current study, TT homozygous mutation was associated with severe asthma.

MDR1 gene polymorphism and genotype distribution

C3435T polymorphism decreases the expression of P-glycoprotein and this expression is highly variable between individuals and between different ethnic groups [23]. In the studies made with Turkish population, similar results were found. In the study of Bebek et al [23] made with 174 healthy adults, C and T allele frequencies were found as 51% and 49% respectively. And genotype distribution was found as %28.2 CC, 46% CT and 25.8% TT. They did not find any linkage between sex and genotype. In current study, wild (CC), heterozygous (CT) and homozygous (TT) polymorphisms were found respectively as 36.2%, 50% and 13.8% at healthy controls. Similar to previous study, C and T allele frequencies were found as 59.3% and 40.7 % respectively. In addition, in current study, there was no difference in healthy control group in terms of sex.

MDR1 gene polymorphism and gender

In children and early adolescents, asthma is more common in boys [2]. In adolescence, the pattern changes and asthma is reported more in girls. After childhood, asthma is more severe in females than in males, and is underdiagnosed and less treated in female adolescents. Females with asthma have more symptoms and worse quality of life than men [24]. However, of these differences about gender have not been fully explained. It may result from differences in sensation of airflow obstruction, increased bronchial hyper reactivity in females [25]. In addition hormonal changes and gender-specific differences in environmental exposures such as tobacco smoke have all been considered as potential causes [2,24,25]. Similar to literatures, however severe asthma was diagnosed more in the girls in current study. In addition homozygous mutation was seen more in the girls again. Medical staff has to be careful on this point. It may be suggested that specific asthma treatment should be planned according to gender especially for female patients.

Limitation of study: When we searched the literature, we could not find a study like this in asthmatic children previously. Therefore, the number of cases may be less in current study, while it is thought that this study may form an idea for further large scale studies. In addition, expression of MDR1 gene polymorphism may differ among various ethnic groups. In order to understand the disease more, there is a need to work with different ethnic groups in a larger sample size.

Conclusions: There was no statistical difference between asthmatic child patients and controls in MDR1 gene polymorphism. However, homozygous polymorphism was found more in severe asthmatic group than mild and moderate persistent groups. This difference was not different at moderate and mild persistent groups as compare to control group. So, it may be said that the difference resulted from severe asthmatic patients. And this information helps us to rank the patients in terms of

asthma by looking MDR1 gene when the patient was diagnosed as asthma. Hence, it can be concluded that treatment of patients, especially with crucial degree may begin earlier and its long-term pursuance can be made. As a result, protection of the patient against chronic complications of asthma may be provided. By doing this, attacks of the patient may be diminished and overcome easily.

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Competing interests

The authors declare that they have no competing interests.

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