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ORIGINAL ARTICLE

Methylenetetrahydrofolate Reductase gene polymorphism in children with allergic rhinitis

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Abstract
Background: Methylenetetrahydrofolate Reductase (MTHFR) polymorphisms by impairing folate metabolism may influence the development of allergic diseases. The results of studies evaluating the relationship between MTHFR polymorphisms and atopic disease are controversial. The aim of this study was to investigate the association between the polymorphisms of C677T and A1298C for MTHFR gene and allergic rhinitis (AR) in children.
Methods: Ninety patients followed up with diagnosis of allergic rhinitis in our clinic and 30 children with no allergic diseases were included in the study. All participants were genotyped for the MTHFR (C677T) and (A1298C) polymorphisms. Vitamin b12, folate and homocysteine levels were measured.
Results: The mean age of patients was 9.2 ± 2.9 years; 66.7% of the patients were male. There was no significant difference between patient and control groups regarding gender, age and atopy history of the family ($p > 0.05$). The frequency of homozygotes for MTHFR C677T polymorphism in the patient and control groups was 3.3% and 10%, respectively. The frequency of homozygotes for MTHFR A1298C polymorphism among groups was 26.7% and 16.7%, respectively. The association between allergic rhinitis and polymorphisms of C677T and A1298C for MTHFR gene was not statistically significant in patients compared with controls ($p > 0.05$). There were no statistically significant differences between the patients and the control group in terms of serum vitamin b12, folate and homocysteine levels ($p > 0.05$).
Conclusion: We found no evidence for an association between allergic rhinitis and polymorphisms of C677T and A1298C for MTHFR gene in children. Further studies investigating the relationship between MTHFR polymorphism and AR are required.

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Introduction

Allergic rhinitis (AR) is a disease developing as a result of immunoglobulin (Ig) E response to allergens in the nose and characterized by symptoms such as nasal congestion, flow, rash, and sneezing. These symptoms occur during two or more consecutive days for more than 1 h on most days. Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Patients from all countries, all ethnic groups, all socioeconomic conditions and of all ages suffer from allergic rhinitis. The prevalence of allergic rhinitis was found to be around 25% in the general population in Europe. Allergic rhinitis is a multifactorial disease induced by gene-environment interactions.[1]

Methylenetetrahydrofolate Reductase (MTHFR) is an important enzyme for folate metabolism and DNA methylation. This enzyme catalysis 5,10-methylenetetrahydrofolate's conversion to 5-methyltetrahydrofolate (5-methyl-THF). MTHFR gene is mapped on chromosome 1 at p36.3 region in humans. There are two of the well-defined single nucleotide polymorphisms (SNP) on the MTHFR gene. These are C677T and A1298C. The C677T polymorphism of MTHFR causes the alanine amino acid to convert into valine at code 222. The conversion occurs at exon 4 of MTHFR protein consisting of 656 amino acids and affects N-terminal catalytic region. In individuals with homozygote TT genotype, it is known that the enzyme activity is reduced and plasma homocysteine levels increase since homocysteine is unable to convert into methionine. The A1298C polymorphism of MTHFR results in a glu429-to-ala (E429A) substitution. Whereas the C677T transition occurs within the predicted catalytic domain of the MTHFR enzyme, the A1298C transition is located in the presumed regulatory domain. The A1298C polymorphism of MTHFR resulted in decreased MTHFR activity, which was more pronounced in the homozygous than heterozygous state.[2]

Lack or excess of folate which plays a role in DNA synthesis may affect gene expressions. Development and differentiation of the immune system occur through epigenetic mechanisms. Folate may change gene expression during the early development phase and therefore it may affect development of allergic phenotype.[3] A diet with high methyl content during pregnancy has been shown to cause allergic asthma phenotype through epigenetic mechanisms in an animal experimental study.[4] Results of studies investigating the correlation between use of folate during pregnancy and development of allergic diseases during childhood are contradictory. There are studies showing that high folate uptake during pregnancy increases allergic diseases (particularly atopic dermatitis (AD) and asthma) during childhood[5–8] as well as other studies showing that high folate uptake during pregnancy does not affect.[3,9–11] or decreases allergic diseases during childhood.[12] In studies where polymorphism on the MTHFR gene was assessed in patients with asthma and allergic rhinitis, TT allele carrier patients were found to have asthma at a higher rate,[13,14] whereas no relation was found in one of the studies.[15] In those studies investigating the relationship between MTHFR and atopic diseases, mainly the relations of asthma and AD were assessed. In the study conducted only on adults (>15 years), it was assessed with respect to AR.[15]

In the current study, we aimed to describe the association between AR and the polymorphisms of C667T and A1298C for the MTHFR gene.

Methods

Ninety patients followed up with diagnosis of allergic rhinitis in the Pediatric Immunology and Allergy clinic of Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital, and 30 children with no allergic diseases were included in the study. Patients were prospectively evaluated through January 2013–June 2013. Detailed allergic disease histories of patients were obtained. Patients were inquired for age, consanguineous marriage, atopy history of the family and exposure to tobacco smoke. Presence of atopy in the family was considered positive when an allergic disease was present in first degree relatives (mother, father or sibling). The diagnosis of AR was made according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.[1] The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local Ethics Committee of Zeynep Kamil Woman's and Children's Diseases Training and Research Hospital. Consent of all patient families was obtained for participation in the study.

Vitamin B12, folate, and homocysteine levels

Blood samples were taken after an overnight fasting, and vitamin B12, folate and homocysteine were made by using chemiluminescent immunoassay kits (Abbott Laboratories, IL, USA). The reference ranges for vitamin B12 and folate were accepted as 200–900 pg/mL and 5–20 ng/mL, respectively. Homocysteine levels were assessed according to normal values in Turkish children.[16]

MHFTR genotyping

Genomic DNA was isolated from the peripheral blood samples using Magnesia DNA Blood Mini Kit (Anatolia, Turkey). C677T and A1298C of MTHFR mutations were genotyped using Bosphore Kit by Real-Time PCR with Montania 483 (Anatolia, Turkey) according to the guidelines of the manufacturer.

Statistical analysis

All results were analyzed using the SPSS (Statistical Package for the Social Sciences) 15 (SPSS Inc., Chicago, IL, USA) program. Categorical variables were described as percentages and number while continuous variables were expressed as minimum, maximum, and mean $\pm$ standard deviation (SD). Student's t test was used for the comparison of normally distributed variables. Chi-square and Mann–Whitney U-tests were used for non-normally distributed variables. Spearman's correlation test was used for the correlation analyses of non-normally distributed variables. Statistical significance was defined as $p < 0.05$.