



PREVALENCE OF MTHFR GENE 677C>T POLYMORPHISM IN THE PATIENTS WITH PSORIASIS VULGARIS

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ABSTRACT:

The study aimed to investigate the relationship between carriage of 677C>T polymorphism in the gene of methylene tetrahydrofolate reductase (MTHFR) and plaque psoriasis in patients in Bulgaria.

We examined the prevalence of MTHFR C677T genotype in patients with psoriasis, as well as the relationship of the polymorphism with disease severity. Our study covered 63 patients with psoriasis and 98 psoriasis-free control subjects from northern Bulgaria. MTHFR 677C>T genotype was verified by the PCR-RFLP method. There was no significant difference between carriage of TT genotype among the patients and controls: 12.7% versus 10.8% in controls, OR 1.203, (CI 95% 0.465-3.175), $p > 0.05$ respectively. There was a higher PASI score in patients, carriers of TT genotype of MTHFR polymorphism 677C>T than in non-carriers, 28.18 versus 24.87 respectively, but not significant.

Conclusion: Carriage of TT genotype of MTHFR polymorphism 677C>T was not associated with Psoriasis Vulgaris in the northern Bulgarian population when compared to healthy controls.

Keywords: Psoriasis, MTHFR polymorphism 677C>T, PASI, Bulgarian population,

INTRODUCTION

Psoriasis (plaque psoriasis) is a chronic dermatological autoimmune disease with a heavy inflammation component, many comorbidities, and still unclear pathogenesis. 2-3% of the human population is affected. [1] The disease is considered multifactorial, involving many systems of the human body [2] and multigenic, with at least 159 genes involved. One of the investigated genes is a gene of MTHFR. The locus of MTHFR is located on the short arm of chromosome 1 (1p36.3). [3]

The enzyme MTHFR is a glycoprotein of molecular weight 70-77000 kDa [3], its activity depends on the availability of FAD as a cofactor and NAD(P)H as a source of reducing equivalent. [4] The enzyme redistributes folate types in the direction of DNA synthesis or a homocysteine remethylation to methionine. [5]

The folate derivative 5,10-methylenetetrahydrofolate is metabolized to 5-methyltetrahydrofolate for the regeneration of methionine from homocysteine by methionine synthase. [6] Methionine is the main substrate to produce S-adenosyl-Methionine (SAM) - a universal donor of methyl groups for DNA and protein methylation. [7] DNA methylation is a crucial epigenetic mechanism for the regulation of DNA activity. [8]

Twenty four mutations/polymorphisms were discovered in the gene of MTHFR that cause a decrease in enzyme activity. [9] One of the most investigated polymorphisms is a substitution of cytosine for thymine at position 677 of the MTHFR gene, which leads to the formation of the thermolabile form of the enzyme caused by alanine to valine replacement. [10] In a heterozygous state, the polymorphism causes a 30%-40% reduction of the enzyme activity, whereas in the homozygous state, roughly 60%-70%. [11]

In the case of reduced levels of folate, the homozygous MTHFR 677C>T polymorphism is considered harmful. [5] Failure to metabolize 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate could cause a rise of homocysteine levels in plasma. [10] Various diseases are associated with carriage of polymorphism MTHFR 677C>T: vascular diseases, male infertility [12], female infertility, neurological and psychiatric diseases, diabetes, cancers [13], hyperhomocysteinemia which is a risk factor for cardiovascular diseases [14] and psoriasis. [15]

Searches related to the MTHFR 677 C > T gene polymorphism frequency show variation between different populations and regions of the world from 4% to 32%. Moreover, the data on mutation carriage in psoriatic patients varies significantly from the conclusion for the Malaysian population that the MTHFR 677 C > T gene polymorphism and the T allele occurrence were not significantly associated with psoriasis vulgaris [16] to the controversial finding that the T-allele and T-containing genotypes (TT, CT) of MTHFR C677T are significantly linked with psoriasis susceptibility while C-allele and CC genotype not. [17] There are no studies on the frequency of this polymorphism in psoriatic patients

in the Bulgarian population. This fact motivated us to evaluate the role of polymorphism 677C>T in the MTHFR gene in patients with plaque psoriasis in northern Bulgaria.

MATERIALS AND METHODS

Selection and evaluation of Patients

Our study was conducted at the Clinic of Dermatology & Venereology, UMBAL - Pleven, Bulgaria, and the University of Medicine-Pleven, Bulgaria. A total of 63 (51 males and 12 females) patients with plaque psoriasis and 98 (64 males and 34 female) control subjects without psoriasis were selected for the study. All subjects were Caucasian. Psoriasis was diagnosed on the basis of clinical feature and histological verification. The Psoriasis Area Severity Index (PASI) is an index used to express the severity of psoriasis. It combines the severity (erythema, induration and desquamation) and the percentage of the affected area.

For each patient, the Psoriasis Area and Severity Index (PASI) was calculated to determine the severity of the dermatosis based on erythema, induration and desquamation of the plaques and the percentage of affected area of the skin (skin surface). Values above 10 determine a severe form of the disease.

The anthropometric, clinical, and laboratory data were collected for each patient. Patient information, including demographic features, was collected using a questionnaire.

Laboratory methods

BMI was calculated according to the formula: body weight/height² kg/cm².

The patients and control subjects without psoriasis were investigated for the carriage of genotype 677C>T. Blood samples were collected in 6ml serum test tubes with EDTA. The DNA was extracted by the salting out method. MTHFR genotype 677C>T was investigated by the PCR method Combined with Restriction Fragment Length Polymorphism assay (PCR-RFLP). Hinf² restriction endonuclease was used for restriction analysis. [18]

Fasting Blood Glucose (FBG) and triacylglycerol (TAG) were measured by conventional laboratory methods.

Statistical analysis was realized with Statistical Package for Social Sciences (SPSS) version 23.0. and Microsoft Excel. Statistical significance p<0.05 was used.

Written informed consent was obtained from each

participant. The study was approved by the ethics committee of Medical University-Pleven.

RESULTS

We examined the association between psoriasis and the prevalence of MTHFR C677T genotype in the Bulgarian population, as well as the relationship of the prevalence of the polymorphism and disease severity. The demographic data, clinical parameters and disease severity in the PASI index of the patients are displayed in Table 1. The mean age of the patients was 55.06 ± 12.310 years, the age of the diagnosis 38.49 ± 14.15 years, the mean BMI was close to the obesity 29.09 ± 6.023 kg/m², the FBG and triglycerides were in the reference range.

Table 1. Characteristics of patients and controls

DATA Means ± SD	Patients	Controls
Number of subjects	63	98
Gender Male/Female	51/12	64/34
Mean Age years	55,06 ± 12,310	47,53 ± 12,10)
Age of the diagnosis years	38,49 ± 14,15	
BMI kg/m ²	29,09 ± 6,023	26,61 ± 5,213
FBG mmol/L	6,03 ± 1,830	5,24 ± 1,830
Triglycerides mmol/L	1,89 ± 1,172	1,76 ± 1,201
PASI SCORE	25,27 ± 7,88	

The prevalence and statistical data on MTHFR 677C>T genotyping of the patients versus healthy psoriasis free controls are presented in Table 2.

The DNA analysis revealed 52.4% of cases with genotype CC, 34.9% of the cases with genotype CT and 12.7% of the cases with genotype TT, whereas the genotype distribution of controls was 42.2% with genotype CC, 47.1% with genotype CT and 10.7% with genotype TT respectively.

The statistical data: odd ratio, Pearson's Chi-Square, significance interval and exact Fisher probability (p) for the weight of TT genotype as a risk factor for psoriasis was calculated versus healthy controls and was respectively: 12.70% versus 10.80% in controls (OR 1.203, P>0.05).

Table 2. MTHFR 677C>T genotypes and Statistical data on MTHFR 677 T prevalence and in psoriatic patients versus controls

MTHFR 677C>T genotypes	Prevalence in patients %	Prevalence in controls %	Odds Ratio	95% Confidence Interval	Fisher's Exact Test
TT	12.70%	10.7%	1.203	0.456-3.175	>0.05
CT	34.9%	47.1%			
CC	52.4%	42.2%			

There was a difference in the PASI score between the patients depending on the genotype (table 3). It was higher in carriers of TT genotype of MTHFR polymorphism 677C>T 28.18 versus 24.69 in non-carriers. However, because of the high value of standard deviation, it was not significant ($p > 0.05$).

Table 3. PASI index in carriers of MTHFR 677 T as compared to non-carriers

MTHFR 677C>T genotypes	PASI INDEX	Significance ($p > 0.05$)
TT	28.18 ±5.42	$p = 0.2412$
CT+CC	24.69±7.78	

DISCUSSION

The relationship between psoriasis and MTHFR 677C>T polymorphism is still not well-understood. The prevalence of the MTHFR 677C>T polymorphism diverges substantially among different populations. [19] The prevalence of polymorphism in our population is well established, it is roughly 10-12%. Our data have provided a prevalence of 10.8% for the TT genotype in the population. The frequency of the MTHFR 677T allele varies from 4% of the population in Finland, 6.4% in the Netherlands, 8% in Israel, 11.1% in Hungary, 11.8% in France and the Czech Republic and it was found as high as 19.8% in North China, and 32% in Mexico, etc. [20] Variability of its world distribution is related to the availability of vitamins like folic acid (B9), B12, absorption of vitamins, various minerals, essential fatty acids and amino acids that interact with folic acid.

The results on the association of carriage of 677C>T MTHFR gene polymorphism with psoriasis vulgaris in different regions of the world are rather conflicting.

Our data haven't revealed any significant difference between carriage of T genotype among the patients with plaque psoriasis and healthy, non-psoriatic controls (OR 1.203, $p > 0.05$).

Wang et al. had presented the first data on the association of MTHFR 677C>T gene polymorphism with psoriasis vulgaris for the Chinese population. [21] A significant association between MTHFR 677 TT genotype and psoriasis was found as well in the study of the psoriatic patients from the Turkish ethnic groups: CC (35.4%), CT (47.9%) and TT (16.7%); whereas the distribution of in the control group was as follows CC 50.6%, CT 45.5% and TT 3.9%. Moreover, a significant difference between the severity of disease ($p < 0.05$) with respect to the carriage of C677T polymorphism in the MTHFR gene was shown for the Turkish population. [22] These results were confirmed by the study of the Iranian group, postulating that MTHFR

677T allele frequencies in psoriatic patients were significantly higher than in the control group (28.5% vs 18.5%; $p = 0.018$). [19]

Indeed, in the European population, the investigation of the Czech Republic presents a lower carriage of the MTHFR TT allele (10.5%) in patients with plaque psoriasis as compared to controls (11.8%). [23] The results of Weger (Austria) showed that the prevalence of the homozygous TT genotype was not significantly higher in the patients than in controls (15.2% vs 11.7%, $P = 0.24$). [24] These results established for Caucasians are in coherence with our finding for the Bulgarian population that the difference between the prevalence of the homozygous TT in psoriatic patients and the control group is not significant. It looks logical, as these investigated groups belong to the same Caucasian race. The aforementioned results on a higher prevalence of TT allele in psoriatic patients could be related to the geographic specificity of the investigated groups, belonging more to the Asian and Middle East population. Recently a newly published investigation in the same region again confirmed the link between carriage of the T-allele of MTHFR 677T and psoriasis in Saudi patients was stating that carriage of. [25]

The plausible difference in ethnicity was suggested to explain these contradictory findings on MTHFR 677C>T polymorphism.

CONCLUSION

Our results show that carriage of the TT genotype of MTHFR polymorphism 677C>T was not significantly associated with psoriasis vulgaris in the Bulgarian population when compared to healthy controls.

The severity of psoriasis was higher (a higher PASI) in the patients, carriers of TT genotype of MTHFR polymorphism 677C>T than in non-carriers, but the data was not significant. The drawback of our study was the size of the sample. To get more reliable data, the investigation of more patients is needed.

Abbreviations:

MTHFR - Methylene tetrahydrofolate reductase
PASI - Psoriasis Area and Severity Index
PCR - Polymerase chain reaction
RFLP - Restriction Fragment Length Polymorphism
SAM - S-Adenosyl-Methionine
FBG - Fasting blood glucose
TAG - triacylglycerol
BMI - Body Mass Index

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