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Original Article

MTHFR C677T gene polymorphism in patients with coronary heart disease and hypertension treated with enalapril and folic acid: implications for prognosis

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Abstract

We aimed to investigate the effect of the methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism on the prognosis of patients with coronary heart disease (CHD) and hypertension treated with enalapril and folic acid. A total of 540 CHD patients diagnosed by coronary angiography in our hospital were selected. According to whether there was folic acid intervention, they were divided into a folic acid group, a non-folic acid group and a control group. The genotypes of the MTHFR C677T locus were detected. Hcy concentration and the folate content were determined. In folic acid group, enalapril and folic acid tablets were used to reduce blood pressure, and clopidogrel or ticagrelor were selected according to CYP2C19 genotypes. In non-folic acid group, enalapril tablets were used, and clopidogrel or ticagrelor were selected based on CYP2C19 genotyping. Routine treatment without intervention was used in control group. Patients were prescribed standardized drug treatment and were followed up by an outpatient service or by telephone for 12 months after discharge. We found that the number and proportion of MTHFR C677T gene mutations in the folic acid group, non-folic acid group and control group were 150 (83.3%), 142 (78.9%) and 144 (80.0%), respectively. The recurrence rate of cardiovascular events in the folic acid and non-folic acid groups was significantly lower, and the degree of reduction in the recurrence rate of cardiovascular events in the folic acid and non-folic acid groups was significantly different. The concentrations of TG, TC, and LDL-C in folate and non-folic groups were lower, while HDL-C was higher than that in control group. To sum up, screening high-risk populations with genotypes has great significance in improving the clinical outcome of CHD patients with H-type hypertension. Folic acid supplementation improves the compliance rate of patients' blood pressure levels and improves their clinical prognosis as well.

Keywords: Coronary heart disease, Folic acid, Gene polymorphism, Hypertension

1. Introduction

There are approximately 300 million hypertension patients in China, and approximately 1/3 of adults have reached the diagnostic standard of hypertension. Hypertension has become the primary factor threatening human health and promoting cardiovascular and cerebrovascular diseases [1]. However, high blood homocysteine (Hcy) and low folate (FA) are common in Chinese patients with hypertension. The mutation frequency of the C677T locus of the MTHFR gene in folic acid metabolism in the Chinese population is higher than that in other countries. Approximately 3/4 of Chinese hypertension patients have hypercy, so Chinese scholars have proposed the concept of H-type hypertension, that is, hypertension with hyperhcy (Hcy≥10 μM), as an important risk stratification factor for hypertension [2]. Studies have reported that the plasma Hcy level of patients with CHD complicated with type H hypertension is closely related to the severity of damaged coronary arteries [3]. Some studies have found that the T gene mutation of the MTHFR C677T gene in CHD patients is positively correlated with the degree of coronary artery disease, and there are higher Hcy levels and lower FA levels in the plasma of patients with mutated genes. MTHFR C677T has been clearly confirmed to be related to the degree of coronary artery disease and long-term clinical prognosis of CHD patients. However, the existing studies have not provided more precise treatment plans for such patients and carried out clinical research on long-term prognosis. Therefore, the purpose of this study is to use genomics detection and folate intervention to provide personalized treatment for patients to reduce the clinical prognosis of coronary heart disease patients with type H hypertension.

2. Materials and Methods

2.1. General clinical data

A total of 540 CHD patients diagnosed with coronary angiography in our hospital from June 2020 to June 2022 were selected as the study subjects. They were randomly divided into a folic acid group, a nonfolic acid group and a control group, with 180 cases in each group. All subjects signed informed consent before the study.

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Diagnostic criteria: (1) CHD diagnostic criteria: coronary angiography was performed by a professional physician skilled in cardiac intervention. The angiographic results suggested that there was definite coronary artery stenosis ≥ 50%, and CHD was diagnosed. (2) Diagnostic criteria for hypertension: referred to the 2014 guidelines for basic level management of hypertension in China (2014 Edition) and the 8th report of ACC/AHA hypertension National Joint Committee (JNC) on guidelines for treatment of hypertension in adults (JNC 8) in 2014. The diagnostic criteria were systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg. (3) Diagnostic criteria for type H hypertension: Hcy ≥ 10 was screened out in patients with primary hypertension μMol/L as the disease standard.

Inclusion criteria and exclusion criteria: (1) inclusion criteria: coronary heart disease was definitively diagnosed by coronary angiography. According to the diagnostic criteria of hypertension, systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, patients with essential hypertension were definitely diagnosed. Plasma Hcy ≥ 10 μmol/L. (2) Exclusion criteria: Patients with severe liver and kidney dysfunction, hematopoietic system disease, previous history of organ bleeding and other contraindications to antiplatelet, tumor and other consumptive diseases; and other subjects affecting plasma Hcy.

2.2. Methods

A total of 540 patients were routinely tested for biochemical indicators after admission.; Routine use of aspirin, clopidogrel or Tegretol, statins, low molecular weight heparin, ACEI/ARB and β-receptor blockers was prescribed. The use of receptor blockers was adjusted according to the patient's heart rate and blood pressure.

Gene detection (1) ACE gene I/D site detection: The principle of the detection kit was the PCR melting curve method. 1) DNA extraction from samples: EDTA anticoagulant was used to extract DNA according to the operating method of the blood genomic DNA extraction kit of Tiangen company. 2) Sample genotype detection: 2 ml of extracted sample DNA was added to the PCR tube, 18 μl of reaction solution was added, and the PCR tube was placed into the slan-96p fluorescence quantitative PCR instrument. The reaction procedure was set as follows: pre-denature at 95 ℃, 2 min, cycle once, 50 consecutive cycles in the cycle section, 1 cycle in the dissolution section, analyze according to the dissolution coefficient curve, read the TM value of the sample, and judge the DD type of the sample. (2) Detection of the MTHFR gene C677T site: 2 ml of EDTA anticoagulant was added to the sample diluent, DNA was extracted from blood, and then PCR amplification was carried out. By using specific primers and markers, the specificity of the MTHFR gene C677T site was determined by using lateral chromatography analysis technology according to the parameters of the gene amplification instrument of Zhaotianlong Company.

2.3. Determination of biochemical items

2.3.1. Hcy determination

The circulating enzyme method was used to determine the serum Hcy level. The serum obtained by centrifugation was placed into the sample rack of the automatic biochemical analyzer. The analytical conditions of the instrument were set according to the parameters provided by the AU680 instrument and the three-dimensional kit to determine the Hcy concentration in the serum sample.

2.3.2. Folic acid determination

Serum separation from Hcy was determined by chemiluminescence. The instrument parameters were set according to the parameters provided by the Roche E602 automatic chemiluminescence analyzer and the same manufacturer's kit. The operation method was performed according to the instrument and kit instructions to determine serum folic acid.

2.4. Treatment of drugs

In the control group (n=180), patients received routine treatment without intervention. In the folic acid group (n=180), patients orally received enalapril tablets once a time, once a day, and folic acid tablets once a time, once a day, and clopidogrel or ticagrelor were selected according to CYP2C19 genotypes. In the non-folic acid group (n=180), patients only orally received enalapril tablets once a time, once a day, and clopidogrel or ticagrelor were selected based on CYP2C19 genotypes. The drug was administered continuously for 4 weeks.

2.5. Statistical analysis

SPSS 22.0 software was used for statistical analysis. The measurement data did not completely conform to a normal distribution and are expressed as the median ± interquartile range (m ± QR), between which a nonparametric test of group data was used. Among them, the Mann–Whitney U test was used for comparisons between two groups, and the Kruskal–Wallis H test was used for comparisons among three groups. The chi-square test was used to compare the counting data. Hardy-Weinberg equilibrium was used to test the genetic stability. The correlation between blood lipid levels and Hcy levels was analyzed by Spearman's test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of baseline data of subjects

A total of 234 males and 306 females were included, with an average age of 64.5 ± 9.6 years. There was no significant difference in age, sex, blood pressure, smoking, or drug baseline treatment of CHD among the three groups. The constituent ratios of patients with angina pectoris and myocardial infarction in the three groups were similar. There was no significant difference in serum cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, C-reactive protein, uric acid or other biochemical indicators between the two groups of subjects, as shown in Table 1.

3.2. Genotyping of three groups of subjects

MTHFR C677T gene analysis was performed on three groups of selected patients, and two results were obtained, namely, nonmutant (CC type) and T gene mutant (CT+TT type). The number and proportion of MTHFR C677T gene mutations in the folic acid group, non-folic acid group and control group were 150 (83.3%), 142 (78.9%) and 144 (80.0%), respectively, as shown in Fig. 1.

Table 1. Baseline clinical characteristics of patients in each group.

Group	Folate (n=180)	Non-folate (n=180)	Control (n=180)	X^2/t	P
General clinical data					
Age (x±s, years)	63.9±8.4	65.4±9.2	64.3±11.1	0.600	0.536
Male [n (%)]	90 (50)	64 (36)	80 (44)	3.891	0.143
Smoking [n (%)]	12 (6.7)	16 (8.9)	20 (11.1)	1.199	0.549
Diabetes mellitus [n (%)]	60 (33.3)	50 (27.8)	46 (25.6)	2.517	0.284
Cerebral infarction [n (%)]	24 (13.3)	30 (16.7)	12 (6.7)	4.350	0.114
Atrial fibrillation [n (%)]	2 (1.0)	12 (6.7)	0 (0)	9.093	0.011
Biochemical index					
G (x±s, mmol/L)	6.32±2.71	6.37±2.31	6.01±2.11	0.580	0.581
TC (x±s, mmol/L)	4.09±1.01	4.08±1.08	4.28±1.21	0.974	0.402
TG (x±s, nunoI/L)	1.80±1.07	1.83±2.08	1.78±1.10	0.029	0.969
HDL (x±s, mmol/L)	1.12±0.33	1.21±0.83	1.11±033	1.015	0.380
LDL (x±s, mmol/L)	2.41±0.83	2.28±0.78	2.50±1.01	0.934	0372
CRP (x±s, mg/ L)	8.15± 19.74	7.67±23.49	6.81 ±20.07	0.080	0.920
UA (*x±s,* umol/L)	292.42±76	308.77 ±106	302.79±92.40	0.724	0.461
CR (x±s, umol/L)	74.1±17.64	81.26±23.30	82.1±27.43	3.247	0.055
Drug use [n (%)]					
Aspirin	180 (100)	180 (100)	180 (100)	—	—
Clopidogrel	78 (43.3)	70 (38.9)	72 (40)	0.399	0.819
Ticagrelor	101 (56.7)	110 (61.1)	108 (60)	0.399	0.819
Isosorbide mononitrate	130 (72.22)	140 (77.78)	134 (74.44)	0.747	0.688
Rosuvastatin	180 (100)	180 (100)	180 (100)	—	—
Low molecular weight heparin calcium	180 (100)	180 (100)	180 (100)	—	—
ACEI/ARB	132 (73.33)	136 (75.56)	142 (78.89)	0.770	0.680
Metoprolol sustained release tablets	126 (70.0)	130 (72.22)	132 (74.16)	0.256	0.880

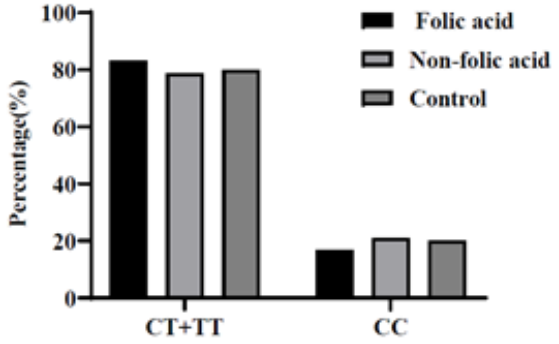

Fig. 1. Genotyping of three groups of subjects.

3.4. Recurrence of cardiovascular events in the three groups after 12 months

In the follow-up and observation of the following 12 months, in the folic acid group, there were 4 cases of recurrent acute myocardial infarction, 12 cases of recurrent angina pectoris, 8 cases of blood pressure control failure, and a total of 18 cases of recurrent cardiovascular events, including angina pectoris, acute myocardial infarction, cerebrovascular accident, etc., accounting for 10.0%. In the non-folic acid group, there were 2 deaths, 9 recurrent angina pectoris, 3 recurrent myocardial infarction, and 20 patients whose blood pressure control did not reach the standard. There were 34 recurrent cardiovascular events in total, including angina pectoris, acute myocardial infarction, and cerebrovascular accidents, accounting for 18.9%. In the control group, 8 cases were lost to follow-up, 2 cases died, 34 cases suffered from recurrent angina pectoris, 8 cases suffered from recurrent myocardial infarction, 36 cases failed to reach the standard of blood pressure control, and a total of 50 cases suffered from recurrent cardiovascular events, including angina pectoris, acute myocardial infarction, cerebrovascular accident, etc., accounting for 29.1%. The follow-up results showed that the recurrence rate of cardiovascular events in folic acid and non-folic acid groups treated with gene-optimized drugs was significantly reduced, and there was a significant difference between folic acid and non-folic acid groups in reducing the recurrence rate of cardiovascular events ($P < 0.05$), as shown in Table 2.

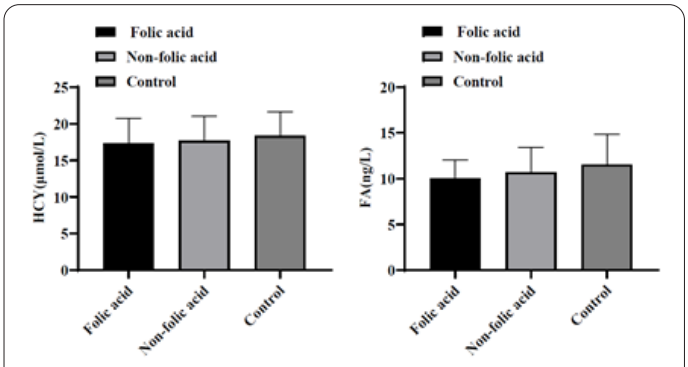

Fig. 2. Plasma HCY and FA levels of three groups of subjects.

Table 2. Recurrence of cardiovascular events in the three groups after 12 months.

Events	Folate (n=180)	Non-folate (n=180)	Control (n=90)	X^2	P
death	0	4 (2.22)	2 (1.11)	2.022	0.364
Recurrent angina	14 (6.67)	18 (10.00)	34 (18.89)	6.878	0.032
Acute myocardial infarction	4 (2.22)	6 (3.33)	8 (4.44)	0.690	0.708
In stent restenosis	0	6 (3.33)	2 (1.11)	3.553	0.169
cerebral apoplexy	0	2 (1.11)	6 (3.33)	3.553	0.169
Massive hemorrhage	0	0	0	-	-
Blood pressure not up to standard	8 (4.44)	20 (11.11)	36 (20.00)	10.494	0.005
Total cardiovascular events	18 (10.0)	34 (18.9)	50 (29.1)	9.283	0.010

3.5. Comparison of blood lipid levels among the three groups of subjects

The blood lipid levels of the three groups were different. The results showed that the concentrations of TG, TC, and LDL-C in the folate and non-folate groups were lower, while HDL-C was higher than that in the control group ($P < 0.05$), as shown in Fig. 3.

4. Discussion

Genetic genes are the most important determinants of each individual's response to drugs. Therefore, in recent years, the detection of individual drug genomes has become an important way to evaluate drug reactions, effectiveness and side effects and thus has a predictive effect on the individualized drug use of patients with different genotypes.

In this study, the MTHFR C677T gene was detected in patients with coronary heart disease and type H hypertension, and the mutation gene phenotype was screened. The results showed that the number and proportion of MTHFRC677T gene mutations in 540 selected patients were 436 (80.7%). It was revealed that there was a high mutation rate of the MTHFRC677T gene in this region, and CYP2C19 gene detection showed that there were 320 cases (59.3%) of gene mutations. Subsequently, the drug treatment was optimized, and a 12-month follow-up was conducted. The results showed that selective drug therapy based on gene phenotype could significantly reduce the risk of recurrent cardiovascular events and improve the effectiveness of drug therapy. At the same time, folic acid treatment was added to increase the plasma FA level of patients to reduce Hcy levels and further reduce the long-term clinical prognosis of CHD patients with type H hypertension.

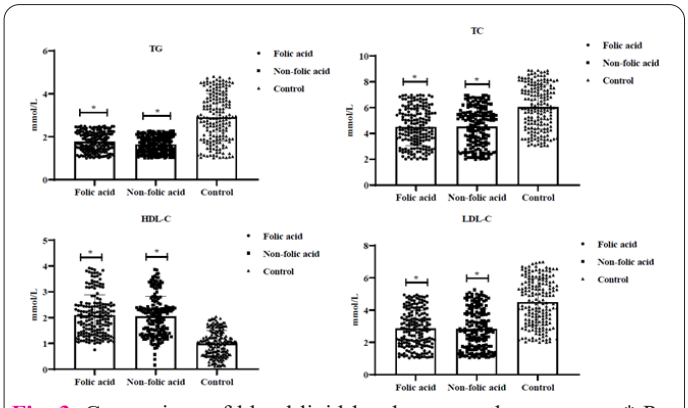

Fig. 3. Comparison of blood lipid levels among three groups. * $P < 0.05$, compared with control group.

Previous reports at home and abroad have found that high HCY levels are considered to be relatively independent cardiovascular disease risk factors, and essential hypertension is also associated with an increased risk of cardiovascular-related diseases. Moreover, these two high-risk factors interact to induce cardiovascular and cerebrovascular events, producing a chain reaction[4]. Therefore, CHD patients with type H hypertension have a higher risk of cardiovascular disease. Gene mutation is the main factor affecting Hcy metabolism in vivo. At present, the MTHFR gene is the most reported gene, and the C677T site in the MTHFR gene is considered to be the key to affecting enzyme activity[5, 6]. Previous studies have suggested that the MTHFR C677T gene polymorphism is related to the incidence of type H hypertension[7], but some studies have reported that in patients with secondary hypertension excluded, the incidence risk is not related to the genes that affect homocysteine metabolism in vivo (MTHFR C677T and MTHFR A1298C) [8]. The results of this study show that there is a high mutation rate of the MTHFRC677T gene in this region. Emphasizing the importance of MTHFRC677T gene detection has more positive clinical significance for most hypertensive patients to reduce the incidence rate of cardiovascular disease.

As a sulfide of Hcy, cystathionine is an important intracellular antioxidant. Previous studies have shown that the level of cystathionine in the plasma of patients with cardiovascular disease is significantly increased. Recently, Dhar I et al. conducted two independent cohort studies on chronic coronary artery disease and acute coronary syndrome, indicating that the plasma cystathionine level of CHD patients not only significantly increased in patients with chronic coronary artery disease but was also related to the increased risk of acute myocardial infarction. The mechanism may be related to cystathionine changing the redox homeostasis of endothelial cells[9, 10]. At the same time, the level of Hcy's active metabolite plays a leading role in the inhibition and degradation of NO in the circulatory system, while NO can promote vasodilation, reduce the invasion and adhesion of platelets to vascular endothelial cells, prevent smooth muscle proliferation, inhibit leukocyte adhesion and the expression of proinflammatory cell genes, and improve the level of low-density lipoprotein cholesterol (OX-LDL) in plasma. Therefore, the increase in Hcy levels is considered to increase the risk of cardiovascular disease, and its mechanism may be related to endothelial cell toxicity, proinflammatory cell activation and procoagulant effects. However, in subsequent trials, correcting Hcy levels did not have a positive effect on the treatment of cardiovascular disease[11]. Gao Xia et al.

can significantly reduce the plasma Hcy level of patients, adjust the anti-platelet aggregation function of vascular endothelium, delay the progression of atherosclerosis in CHD patients with type H hypertension, and reduce the risk of cardiovascular events by applying FA intervention to patients with type H hypertension[12]; COTLARCIUC et al also confirmed that folic acid supplementation can significantly reduce plasma Hcy [13, 14].

In a further study, this study compared the blood lipid level of hypertensive patients with three genotypes of MTHFR C677T and found that the blood lipid level in the hypertensive group was different among different genotypes, among which TC, TG, LDL-C, concentration TT>CC, HDL-C concentration TT<CC ($P>0.05$). Among them, the blood lipid indexes between the TT and CT groups and the CT and CC groups were not completely different and may not show differences due to sample size and other factors. However, the current results reflect that the levels of HDL-C and apoAI blood lipid indicators in homozygous TT-type hypertensive patients decrease more significantly, and the levels of other blood lipid indicators increase more significantly. In different populations, the correlation between the MTHFR C677T polymorphism and plasma lipid mass spectrometry has been evaluated in several studies. However, the results are not consistent. In a domestic study, 780 white pants Yao subjects and 686 Han subjects were randomly selected for research and analysis. The serum TC and LDL-C levels of T allele carriers were higher than those of non-T allele carriers[15]. This result is consistent with the results of this study. Other scholars at home and abroad have reported similar results[16, 17]. However, in 2000, Spiridonova et al. showed that MTHFR gene polymorphisms were not related to changes in TC, VLDL-C, LDL-C, HDL-C and TG levels[18]. This is consistent with the existing research results[19]. A large number of studies show that the distribution of the MTHFR C677T polymorphism is affected by region and ethnicity[20-25]. This study has not yet ruled out the effect of taking lipid-lowering drugs. Therefore, the inconsistency of research results is likely to be affected by regions, population distribution, use of lipid-lowering drugs, sample size, etc.

5. Conclusion

In summary, there is a high incidence of the MTHFR C677T gene polymorphism in this region. Therefore, screening high-risk populations by detecting gene types is of great significance to improve the clinical prognosis of coronary heart disease patients with type H hypertension in this region. At the same time, based on the high recurrence rate of cardiovascular events in coronary heart disease patients with local type H hypertension, folic acid supplementation can not only further improve the compliance rate of patients' blood pressure levels but also have a positive role in improving the clinical prognosis of patients.

Conflict of Interests

The authors declare no competing interests.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

We have received approval from the Ethics Committee of First People's Hospital of Lanzhou and Second Provincial People's Hospital of Gansu.

Informed Consent

We have received informed consent from the Ethics Committee of First People's Hospital of Lanzhou and Second Provincial People's Hospital of Gansu.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

ZL contributed to the study conception and design. Experimental operation, data collection and analysis were performed by ML and WX. The first draft of the manuscript was written by ML. All authors commented on previous versions of the manuscript.

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