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Correlation study of *CYP2C19* gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou region

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Abstract

This study conducts a correlation exploration of *CYP2C19* gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou Region.

A total of 270 Han Chinese patients with cerebral infarction, who were hospitalized in our hospital from January 2016 to January 2018, are selected. These patients were divided into 2 groups, clopidogrel resistance group (n = 60) and clopidogrel sensitive group (n = 210). According to the TEG results, the *CYP2C19* gene polymorphism detection was carried out by using the PCR-RFLP method, while IL-6 level in the patient's blood was measured by using the ELISA method.

The resistance group occupies 22.22%. The platelet inhibition ratio of the resistance group was 23 ± 7%, which was significantly lower than that of the sensitive group (65 ± 13%), and the difference was statistically significant ($P < .05$). The Logisitic regression analysis revealed that the history of diabetes, history of high blood pressure, increase in low density lipoprotein and *CYP2C19* mutant gene were independent risk factors of clopidogrel resistance. After treatment, the serum IL-6 level of patients in the resistance group was 17.21 ± 0.98 ng/L, which was significant higher than that of patients in the sensitive group (11.21 ± 0.68 ng/L), and the difference was statistically significant ($P < .05$).

Patients with cerebral infarction in Guizhou region have a higher occurrence rate of clopidogrel resistance. Clopidogrel resistance not only will weaken the anti-inflammatory action of the drug, but also correlates with the patient's *CYP2C19* mutant gene and blood lipid level.

Abbreviations: ADP = adenosine diphosphate, CT = computed tomography, EDTA = ethylenediaminetetraacetic acid, ELISA = enzyme-linked immunosorbent assay, EM = extensive metabolizer, ITGB3 = integrin β3, MA = maximum amplitude, MRI = magnetic resonance imaging, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PM = poor metabolizer.

Keywords: cerebral infarction, clopidogrel resistance, CYP2C19, gene polymorphism, IL-6

1. Introduction

At present, since clopidogrel can inhibit platelet aggregation, it has become the preferential drug[1–3] for the antithrombotic therapy of acute cerebral infarction. As one of the basic drugs for prevention and interventional therapy for acute cerebral infarction, clopidogrel has become a commonly used anti-platelet aggregation drug in clinic. However, some patients with cerebral arterial thrombosis have clopidogrel resistance, which may be correlated to gene polymorphism and other factors in the clopidogrel metabolism and action process.[4–6] A study reveals[7] that clopidogrel resistance is correlated to cytochrome P450 gene mutation. The enzyme of such gene coding is the key enzyme in the process of the metabolism and catalysis of clopidogrel and approximately 45% is mediated by the CYP2C19 protein. Hence, *CYP2C19* gene polymorphism plays a decisive role in the efficacy of clopidogrel. Meanwhile, CYP2C19 realizes the selective binding with the receptor (P2Y12) of platelet surface adenylatecyclase coupling adenosine diphosphate (ADP), thereby realizing the irreversible selective inhibition of platelet aggregation induced by ADP. Hence, the mutation of any link will weaken the inhibiting effect of clopidogrel upon platelet aggregation, thereby causing the thrombosis.[8,9] At present, the use of clopidogrel in Guizhou region is more common, and patients with clopidogrel resistance are not in the minority, but the study in this

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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direction is still at a blank stage. The present study aims to discuss the correlation of *CYP2C19* gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou region, providing new evidence for the individual prevention and treatment of patients with cerebral stroke in Guizhou region from the perspective of individual difference, biochemistry and genetic variation.

2. Data and methods

2.1. General data

The present study selected 270 Han Chinese patients with cerebral infarction, who were hospitalized in our hospital from January 2016 to January 2018. Among these patients, 148 patients were male and 122 patients were female, and the age of these patients ranged within 39 to 85 years old, with the average age of 63.5 ± 10.4 years old. Furthermore, the course of disease was 6 to 72 hours, and the average course of disease was 38.2 ± 11.3 hours. Case inclusion criteria: The above cases meet the related standards[10] under the *Chinese Guidelines for Secondary Prevention of Cerebral Ischemic Stroke and Transient Ischemic Attack 2014*, and were verified by head computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria: Patients who suffer from the serious liver, kidney and hemopoietic system diseases and patients who did not use other drugs that could affect platelet function within 1 month. In addition, in order to further avoid the interaction of drugs, the patient did not take other drugs, except for clopidogrel and atorvastatin, during the study period.

This study was approved by the Ethics Committee of Guizhou Aerospace Hospital. Written informed consent was obtained from all participants.

2.2. Methods

2.2.1. Data collection. The age, gender, smoking, high blood pressure, diabetes, heart disease and other information of the selected patients were recorded at admission. Venous blood was collected from the patient at an empty stomach on the 2nd day after admission for the determination of blood lipid, fasting blood glucose, hemorheology (platelet aggregation rate), blood uric acid, homotype cysteine and other indicators. The smoking standard was set to be at least >5/d for more than 3 consecutive months. After the first collection of venous blood, the patient stopped taking other anti-platelet aggregation drugs, but took 75 mg of clopidogrel (Sanofi, USA) once a day for 10 consecutive days, and took other lipid-regulating drugs for treatment during the drug treatment period.

2.2.2. Determination of the platelet aggregation rate. A 5000 type thrombelastogram coagulation analyzer (TEG, Heamoscope, USA) was selected, and the reagent included kaolinite (including 1% Kaolin solution), ADP and an activator, and all these were bought from Heamoscope (USA). Two ml of venous blood was collected and placed in a tube containing an anticoagulant on the morning of the second day after the patient received the clopidogrel for 10 days, and monitoring analysis was conducted for 2 hours after blood collection using a thrombelastogram coagulation analyzer. The maximum amplitude (MA) in the checking process of the thrombelastogram coagulation analyzer was the maximum amplitude on the TEG for indicating the maximum hardness or strength of the blood clot. Fibrinogen and platelet were the main influencing factors of MA. MA can be divided into $MA_{Thrombin}$, MA_{ADP} and MA_{Frbrin}, according to the different activators in blood. $MA_{Thrombin}$ represents all the fibrinogens and thrombins. MA_{ADP} is part of a platelet, including platelets not inhibited by the ADP inhibitor and all of fibrinogens. MA_{Frbrin} is the fibrinogen. Platelet aggregation inhibition ratio (%) = MA_{ADP}-MA_{Frbrin} / $MA_{Thrombin}$-MA_{Frbrin} ×100%. Evaluation criterions: 20 pmol/L of ADP is the inducer. For the inhibition of platelet aggregation, compared with the baseline value, a value of <40% represents platelet aggregation clopidogrel resistance, while a value ≥40% represents clopidogrel sensitive.

2.2.3. CYP2C19 gene polymorphism testing

2.2.3.1. Commonly used reagents and instruments. The blood genome DNA isolation kit was bought from TIANGEN Biotech (Beijing) Co., Ltd. The human CYP2C19 genetic testing kit (PCR fluorescence probe method) was bought from Wuhan YZY Medical Science and Technology Co., Ltd. The CYP2C19 genetic testing kit and identifying and reading instrument were bought from Shanghai BaiO Technology Co., Ltd. The real-time Quantitative-PCR instrument 7500 type was bought from ABI (USA).

2.2.3.2. CYP2C19 genotype testing. *CYP2C19* gene polymorphism testing was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The PCT testing method: Two ml of blood sample was collected at an empty stomach on the day when the patient took the drug, placed in an ethylenediaminetetraacetic acid (EDTA) anticoagulant tube, stored in a refrigerator at a temperature of 4°C, and the DNA was extracted within 24 hours. The blood genome DNA isolation kit is used to extract the patient's DNA sample (A260/A280 of DNA IS 1.8–2.0, and the concentration was 5–15 ng/μl). Then, this was stored in a refrigerator at a temperature of -20°C, and tested within 24 hours. Two μl of the DNA sample was added to the CYP2C19 genetic testing PCR reaction tube (CYP2C19 *2: forward primer; 5′-ATFACAACCAGAGC-TTGGC-3′, reverse primer 5′-AGCAITACTCCTTGACC-TGTT-3′; CYP2C19 *3: forward primer; 5′-CCATTATTTAAC-CAGCTAGGC-3′, reverse primer 5′-AATGTACTTCAGGG-CTTGG-3′), and the test was carried out (AB 7500) as required.

2.2.4. Interleukin-6 (IL-6) testing. Enzyme-linked immunosorbent assay (ELISA) is used to determine the IL-6 level of the patient in the venous blood collected twice at an empty stomach. The ELISA kit was bought from R&D (USA).

2.3. Observation indicators

The allele frequency, genotype and serum IL-6 level of the *CYP2C19* gene polymorphism of patients with cerebral infarction in the clopidogrel resistance group and clopidogrel sensitive group are observed, and the risk factors of clopidogrel resistance of patients with cerebral infarction were analyzed.

2.4. Statistical method

The analysis for all data was performed using statistical software SPSS 19.0. The count data were presented in percentage (%). The chi-square (χ^2) test or Fisher exact rate test (less sample) was conducted, the measurement data were presented as mean ± standard deviation ($\bar{x} \pm SD$), and *t*-test (pairing or independent sample) was carried out. The analysis of risk factors was

Table 1

Comparison of two groups of general information.

Index	Clopidogrel resistance group (n = 60)	Clopidogrel sensitive group (n = 210)	t/χ^2	P
Male/Female (n)	33/27	105/105		
Age (Y)	64.4 ± 9.9	63.1 ± 11.2	0.812	.417
High blood pressure (n)	51	181	0.055	.815
Diabetes (n)	9	29	0.055	.815
Total cholesterol (mmol/l)	4.8 ± 1.3	4.6 ± 1.1	1.191	.235
Triglyceride (mmol/l)	1.5 ± 0.7	1.5 ± 0.8	0.000	1.000
Low-density lipoprotein (mmol/l)	3.5 ± 0.8	3.2 ± 0.4	3.156	.002
High-density lipoprotein (mmol/l)	1.1 ± 0.3	1.2 ± 0.4	1.796	.074

performed using logistic regression analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Single factor analysis

Among these 270 patients, 60 patients had clopidogrel resistance (clopidogrel resistance group), accounting for 22.22%, while 210 patients were clopidogrel sensitive (clopidogrel sensitive group), accounting for 77.78%. The platelet inhibition ratio of the clopidogrel resistance group was 23 ± 7%, which was significantly lower than that of the clopidogrel sensitive group (65 ± 13%). The low density lipoprotein level of the clopidogrel sensitive group was 3.2 ± 0.6 mmol/l, which was significantly lower than that of the clopidogrel resistance group 3.5 ± 0.8 mmol/l. Hence, the difference was statistically significant ($P < .05$). For the other indicators of the patients in these 2 groups, such as gender, blood lipid and chronic disease history, the difference was not statistically significant, refer to Table 1.

3.2. Logistic regression analysis

The factor with a significant difference through the single factor comparison of the general data of these 2 groups was taken as the independent variable, and the possibility of occurrence of clopidogrel resistance was taken as the dependent variable. These 2 variables were substituted into the logistic regression equation. Upon logistic regression analysis, history of diabetes, history of high blood pressure, increase in low density lipoprotein and CYP2C19 mutant gene were the independent risk factors of clopidogrel resistance (Table 2).

3.3. CYP2C19 typing testing results

The CYP2C19 polymorphic site *2 and *3 of patients in the present study conform to the Hardy-Weinberg law of genetic equilibrium, and these selected objects have group representativeness. CYP2C19 genetic typing test results: The DNAPCR testing and fluorescent gene chip test results are presented in Figure 1.

3.4. CYP2C19 genotype frequency and frequency comparison of these 2 groups of patients

The *1/*1 genotype of the clopidogrel sensitive group accounted for 51.42%, which was higher than that of the resistance group (20.00%). The *2/*2 allelotype of the clopidogrel sensitive group accounted for 1.42%, which was lower than that of the resistance group (35.00%), and the difference was statistically significant ($P < .05$), refer to Table 3.

3.5. Comparison of CYP2C19 allele frequency in these 2 groups of patients

The *1 allele frequency of the clopidogrel sensitive group accounted for 82.85%, which was higher than that of the resistance group (40.00%). The *2 allele frequency of the clopidogrel sensitive group accounted for 14.28%, which was lower than that of the resistance group 55.00%, and the difference was statistically significant ($P < .05$), refer to Table 4.

3.6. Comparison of IL-6 levels in these 2 groups of patients before and after treatment

After treatment, the serum IL-6 level of patients in the clopidogrel resistance group was 17.21 ± 0.98 ng/L, which was significant higher than that of the sensitive group 11.21 ± 0.68 ng/L, and the difference was statistically significant ($P < .05$), refer to Table 5.

4. Discussion

Clopidogrel is an inactive prodrug. As a thienopyridine antiplatelet prodrug, it forms an active metabolite by depending on the P450 enzyme action of cytochrome in the liver, and

Table 2

Logistic regression analysis.

Index	β	S.E.	Wald	P	OR	OR 95%CI
Gender	0.731	0.232	5.941	.543	2.24	0.178~8.256
Age	1.062	0.325	10.458	.571	1.03	0.327~7.148
Smoking	1.952	0.422	31.579	.092	16.02	4.723~35.481
Diabetes	0.941	0.279	11.448	.012	4.69	1.049~8.761
High blood pressure	0.653	0.328	13.001	.013	6.68	3.334~9.297
CYP2C19*2 gene mutation	0.727	0.476	10.713	.024	4.43	1.241~8.216
Low-density lipoprotein increase	0.616	0.384	2.539	.023	6.12	3.356~23.569

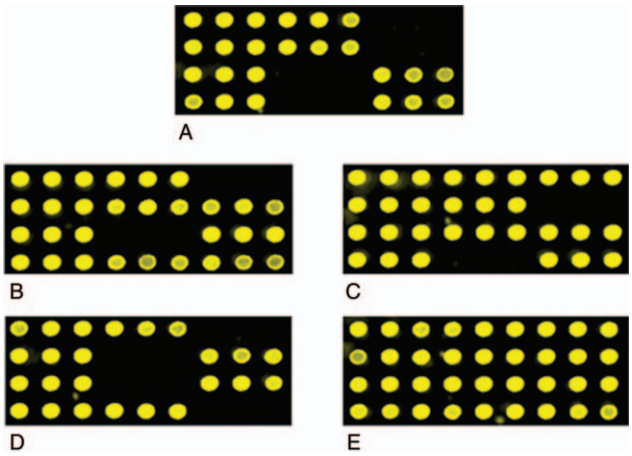

Figure 1. The DNAPCR testing and fluorescent gene chip test results.

through oxidation, hydrolysis and other enzymatic reactions after oral absorption, thereby giving play to the role of an anti-platelet aggregation drug.[11–13]

4.1. CYP2C19 gene polymorphism and clopidogrel resistance in Han Chinese patients with acute cerebral infarction in Guizhou region

Cytochrome P450 is an important drug metabolic enzyme system in the human liver, and the main superfamily enzyme system that participates in the drug phase I metabolic reaction, which carries out the mediation of drug oxidation, reduction, or hydrolysis reaction.[14] The liver cytochrome P450 enzyme system converts clopidogrel into an active metabolite for the binding with ADP receptor P2Y12 on the platelet membrane, thereby interdicting the fibrinogen receptor mediated by ADP. That is, it is activated by the glycoprotein GPIIb/IIIa compound of integrin β3 (ITGB3) gene coding. Thus, platelet aggregation is prevented.[15] The known human CYP super family includes 14 families and 26 subfamilies, and more than 50 subtypes with catalytic function participate in the metabolism of more than 70% of clinical drugs. CYP1, CYP2 and CYP3 are the main families that participate in the drug metabolism, CYP3A4, CYP3A5 and CYP2C19 jointly participate in the metabolism of clopidogrel, and CYP2C19 (mainly *2) occupies the leading role.[16] The CYP2C19 enzyme protein plays a leading role in the metabolism and catalysis of clopidogrel and the *CYP2C19* gene for coding such enzyme protein represents the polymorphism expression in the human body. Among Asians, the most commonly used genotype is CYP2C19*1, CYP2C19*2 and CYP2C19*3, *5 and *6, and the first and foremost non-functional allele is *2 and *3. The frequency of occurrence of CYP2C19*2 is higher than that of CYP2C19*3.[17] Among the above genotypes, the activity of an enzyme not carrying the *2 and *3 allele coding was the highest,[18] namely, *1/*1, which was defined as the extensive metabolizer (EM). Furthermore, the activity of an enzyme carrying 2 non-functional alleles (*2/*2, *2/*3 and *3/*3 coding) was the lowest, which was defined as the poor metabolizer (PM).[19] The activity of an enzyme carrying a non-functional allele (*1/*2 or *1/*3 coding) was between these 2, which was defined as the intermediate metabolizer. The carrying rate of the most common non-functional gene CYP2C19*2 among Asians can reach up to 55% to 70%, and the carrying rate of the non-functional gene CYP2C19*3 was approximately 10% to 20%. The other gene mutation CYP2C19*17 can increase the activity of the CYP450 enzyme, and *1/*17 or *17/*17 was defined as the strong metabolism. Therefore, the daily acceptable daily intake of

Table 3

CYP2C19 genotype frequency and frequency comparison of these two groups of patients [n (%)].

Groups	n	*3/*3	*2/*3	*2/*2	*1/*3	*1/*2	*1/*1
Clopidogrel resistance group	60	0 (0.00)	3 (5.00)	21 (35.00)	3 (5.00)	18 (30.00)	12 (20.00)
Clopidogrel sensitive group	210	0 (0.00)	0 (0.00)	3 (1.42)	6 (2.85)	60 (28.50)	108 (51.42)
χ^2		–	3.5393	21.647	0.221	0.015	6.223
P		–	0.059	0.000	0.637	0.901	0.012

Table 4

Comparison of CYP2C19 allele frequency in these two groups of patients [n (%)].

Groups	n	*1	*2	*3
Clopidogrel resistance group	60	24 (40.00)	33 (55.00)	6 (10.00)
Clopidogrel sensitive group	210	174 (82.85)	30 (14.28)	30 (14.28)
X^2		29.178	14.414	3.546
P		.000	.0001	.060

Table 5

Comparison of IL-6 levels in these two groups of patients before and after treatment.

Groups	n	Before treatment IL-6 (ng/L)	After treatment IL-6 (ng/L)	*t*	*P*
Clopidogrel resistance group	20	24.21 ± 1.01	17.21 ± 0.98	22.2446	.0000
Clopidogrel sensitive group	70	24.35 ± 1.11	11.21 ± 0.68	84.4546	.0000
t		0.5069	31.3562		
P		.6135	.0000		

clopidogrel was determined according to the metabolism type. Patients with acute cerebral infarction in the present carry the CYP2C19*2 and CYP2C19*3 alleles, which indicate that these 2 alleles are more common among Han Chinese patients with acute cerebral infarction in Guizhou Region. Hence, the analysis and detection shall be strengthened during treatment. In addition, the CYP2C19*2 allele was positively correlated with clopidogrel resistance, and the proportion of the *2/*2 allelotype of the clopidogrel resistance group was significantly higher than that of the clopidogrel sensitive group, indicating that the mutant genotype occupies a special position in clopidogrel resistance. Therefore, the testing of the CYP2C19*2 allele should be strengthened for patients with acute cerebral infarction when taking clopidogrel.

4.2. Indicative role of the platelet aggregation inhibition ratio for patients with acute cerebral infarction

Genome sequencing has been more and more applied for the prevention and diagnosis of diseases, but the reference value for clinical medication is limited.[20] The present study uses the TEG analyzer to analyze the platelet aggregation of patients. This approach can be performed in real-time, and is dynamic, fast and accurate. Hence, it can test a series of changing process, including blood coagulation, fibrinolytic activity and platelet aggregation.[21] ADP can selectively activate a platelet. Hence, the ADP receptor antagonist can be added in the testing process for testing the platelet aggregation rate.[22,23] The present study applies such testing means to the platelet aggregation of patients with acute cerebral infarction, and these results indicate that the patient's clopidogrel resistance event was positively correlated with the TEG testing results, with a certain reference value.

4.3. Clopidogrel resistance and inflammatory reaction

The study indicates[24] that clopidogrel has the function of anti-inflammatory reaction. The occurrence of clopidogrel resistance is affected by many factors, and the weakening of anti-inflammatory reaction may be one of the mechanisms of clopidogrel resistance. When the immune factor and inflammatory factor of patients with acute cerebral infarction is released, the endogenous cytokine in the cyclic process would increase.[25,26] Then, the infiltration of inflammation cytokines would lead to chronic nonspecific inflammation, which is closely correlated to the occurrence and development of acute cerebral infarction. As an index component correlated to body stress and immunoregulation, IL-6 is the most concerned inflammatory reaction biomarker. IL-6 has many bioactive functions: the promotion of the proliferation of B cell, T cell and fibroblast; the induction of the synthesis of acute phase protein; the participation in body inflammatory reaction.[27] In addition, IL-6 can directly damage the endangium, release the inflammatory medium, increase vascular permeability and cause atherosclerosis. The study on patients with acute cerebral infarction in the present study revealed that clopidogrel can significantly reduce the IL-6 level in the body of patients with acute cerebral infarction within a short term, and the IL-6 level of patients in the clopidogrel sensitive group decreased more, which indicates that clopidogrel resistance not only affects the anti-inflammatory action of the drug, but also weakens the drug's ability of anti-platelet aggregation. The joint action of these 2 may lead to the occurrence of cardiovascular and cerebrovascular adverse events.

4.4. Risk factors and clopidogrel resistance of ischemic stroke

The occurrence mechanism of clopidogrel resistance has not been completely expounded, and its influencing factors can be divided into internal factors and external factors. The external factors include the patient's living habit, medication compliance, and drug-drug interaction, while the internal factors mainly include individual genetic differences. Hence, drug metabolism gene polymorphism is the priority among priorities.[28] The present study also revealed that the frequency of the *2/*2 allelotype and *2 allele in the clopidogrel resistance group was higher than that of the clopidogrel sensitive group. On the Logistic regression analysis, the *CYP2C19* mutant gene is the independent risk factor of clopidogrel resistance, which indicates that the carrying of the mutant gene may weaken the treatment effect of clopidogrel on the patients with acute cerebral infarction. In addition, the history of diabetes and increase in low density lipoprotein are also independent predictive factors of clopidogrel resistance. First, the increase in low density lipoprotein may cause hyperlipemia, and hyperlipemia can promote the activation of platelets and monocytes, as well as the adhesion between platelets and monocytes, thereby leading to clopidogrel resistance.[29,30] Second, the coagulation state in the body of patients with diabetes would increase the risk of arterial thrombosis complication. Especially for patients with type-2 diabetes, the existence of insulin resistance leads to the increase in activity of P2Y12 receptor, which subsequently causes the enhancement of platelet aggregation ability.

In conclusion, patients with cerebral infarction in Guizhou region have a higher occurrence rate of clopidogrel resistance. Clopidogrel resistance not only weakens the anti-inflammatory action of the drug, but also correlates with the patient's *CYP2C19* mutant gene, cerebrovascular disease history and blood lipid level.

Author contributions

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