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Review Article

Clinical and prognostic value of ALDH2 in acute ischemic stroke

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Abstract: Objective: This study set out to investigate the ALDH2 expression in acute ischemic stroke (AIS) and its clinical and prognostic value. Methods: AIS patients treated in Inner Mongolia Forestry General Hospital from November 2016 to November 2018 were selected as group A (n=80), and healthy people were taken as group B (n=50). Clinical data of patients were collected and they received treatment. ALDH2 expression levels (mRNA, protein) in serum of the two groups were detected. Meanwhile, mRNA and protein expression levels of ALDH2 in AIS patients and their recovery under distinct pathological characteristics and pathological conditions were analyzed. Results: ALDH2 expression levels in group A were clearly lower than those in group B. ALDH2 relative expression levels of diabetes patients and those who liked drinking were markedly lower, and there was no remarkable difference in other people. These relative expression levels in serum of patients with large-scale stroke were dramatically lower. And those in serum of patients with moderate and severe cerebral infarction were much lower. ALDH2 expression level in serum, NISS and diabetes can be used as prognostic factors for acute stroke. Simultaneously, in a large range of patients, 59 recovered well and 21 recovered poorly. Conclusion: Decrease and absence of ALDH2 expression level may easily lead to the occurrence, deterioration and area enlargement of AIS. It can be used as a molecular target and prognostic risk factor clinically.

Keywords: ALDH2, acute ischemic stroke (AIS), prognosis

Introduction

Acute ischemic stroke (AIS) is a familiar disease [1], and its risk will increase with age [2]. The cause of this disease is intracranial vascular occlusion caused by atherosclerosis, which in most cases will block a portion of blood flowing to the brain, giving rise to partial cerebral tissue infarction of the brain supplied by these blood vessels [3, 4]. Postoperative complications such as hyperglycemia often occur [5]. Due to its high morbidity and mortality, the treatment of this disease is extremely important [6, 7]. The study of molecular targets for stroke has always been a crucial research direction. One of the molecular mitochondrial aldehyde dehydrogenases (ALDH2) can be used as a related molecular target in stroke [8].

ALDH2 is a part of the stage I oxidase aldehyde dehydrogenase (ALDH) superfamily. Its protein expression level is higher in normal lung and liver, and higher in mitochondria-containing organs such as heart and brain [9]. It is used to metabolize ethanol and detoxify biological and heterogeneous aldehydes, and plays a vital role in the process of cerebral ischemia reperfusion injury, etc. Its insufficient activity tends to increase the risk of cardiovascular diseases [10-12]. It is a prognostic protein in some diseases such as lung cancer and leukemia [13-15]. However, there are not many studies on ALDH2 expression in stroke and its prognostic value. Hence, this study aims to explore the ALDH2 expression in AIS, its clinical and prognostic value, and whether it is suitable for use as a prognostic protein for AIS.

Materials and methods

General information

Eighty patients with AIS treated in Inner Mongolia Forestry General Hospital from November 2016 to November 2018 were selected as group A, and 50 normal physical examination

Table 1. Sequence table of related primers

Factor	Upstream primer	Downstream primer
ALDH2	5'-TGCTATGATGTGTTTGGAGCC-3'	5'-CCCACACTCACAGTTTTCACTTC-3'
GAPDH	5'-ATGTTCGTCATGGGTGTGAA-3'	5'-GGTGCTAAGCAGTTGGTGGT-3'

patients without AIS were selected as group B. Inclusion criteria: patients met the 2018 American Heart Association/American Stroke Association Guidelines for Medical Care Professionals in Diagnosis of Cerebral Stroke Death [16] and it was confirmed to be acute stroke through MRI and CT examination. Patients ages ranged from 50-84 years old. It was their first onset of stroke. Time from onset to treatment was within 6 h. Their family members were informed and they signed an informed consent form. Exclusion criteria were as follows: those with thrombolytic taboo; those who received heparin sodium treatment and oral anticoagulation within 48 h; those with urinary system or gastrointestinal hemorrhage within the past 3 weeks; those with intracranial trauma or surgery history; epilepsy history; those who used immunosuppressive and anti-inflammatory drugs in the past month; those who suffered from inflammatory diseases that had an impact on this study; and those who had mental problems.

Patient treatment

(1) Clinical data indicators of patients were collected: Patients' age, gender, hypertension, hyperlipidemia, diabetes, atrial fibrillation and so on. (2) Treatment methods for patients: They were given basic treatment schemes such as maintaining oxygen inhalation, stable pulse and cardiopulmonary function. We monitored their vital signs and allowed them to use some conventional drugs for antiplatelet, anti-infection, intracranial pressure reduction, neurological function protection, etc. On this basis, they were given aspirin enteric-coated tablets (Shenyang Original Pharmaceutical Co., Ltd., SFDA Approval No.: H20065051) and atorvastatin tablets (Beijing Jarlin Pharmaceutical Co., Ltd., SFDA Approval No.: H19990258) for treatment. They received aspirin enteric-coated tablets 100 mg each time, once a day and atorvastatin 20 mg each time, once a day. The duration of one course of treatment was 14 days, with a total of 2 courses of treatment. Twenty-four hours after treatment, MRI and CT were performed to judge the recovery degree of the patients after treatment. (3) Collection of blood samples of patients: Blood tests were carried out before and 28 days after drug treatment. Fasting was carried out for 12 h before the test, and then blood samples were collected to detect the ALDH2 expression levels and other factors.

Detection methods and analysis indicators

(1) mRNA and protein expression levels of ALDH2 in serum of groups A and B were detected.

mRNA level of ALDH2: It was detected by qPCR. First, the total RNA in the serum was extracted, 50 ml of the serum was put into a 1.5 ml RNAse-free centrifuge tube, and then 0.5 ml of Trizol (Shanghai Yuanye Biotechnology Co., Ltd.) was added. After uniform shaking, 0.5 ml of Trizol was added, and the whole process was left standing for about 0.5 h. A total of 200 μl chloroform was added to every 1 ml Trizol. After rapid shaking and mixing for 30 sec, the mixture was placed on ice for 5 min. Then it was incubated 10 min at 1500× g at 4°C. About 400-600 μl of supernatant was transferred to a new centrifuge tube with a pipette. Soon afterwards, we added isopropyl alcohol 500 μl/trizol 1 ml, covered it up, reversed it repeatedly, mixed it evenly, and let stand for 10 min. We put it into a centrifuge, and set it at 1500× g at 4°C for 10 min. The supernatant was discarded, isopropyl alcohol was absorbed, then 1 ml of 75% ethanol was supplemented, and the mixture was thoroughly mixed. RNA was washed for 10 min with 1500× g at 4°C. The supernatant was discarded, dried naturally for 5-10 min, and 20 μl of DEPC water was added to fully dissolve the total RNA. The concentration and purity of total RNA were detected by ultraviolet spectrophotometer (Beijing Jiayuan Xingye Technology Co., Ltd). RNA with OD260/OD280 ratio between 1.8 and 2.0 was taken, and then cRNA was synthesized by reverse transcriptase and oligonucleotides according to the operation instructions. After that, qPCR was carried out in ABI7500 fluorescence quantitative PCR instrument (Beijing Longyue Biotechnology Development Co., Ltd). The upstream and downstream primers were shown in **Table 1**. It was pre-denatured 5 min at 95°C, then denatured 15 s at 95°C and annealed 30 s at 60°C, for 40 cycles, 60-95°C. The results were compared with the internal reference.

Table 2. General clinical baseline data of groups A and B [n (%)] (X±S)

Group	Group A (n=80)	Group B (n=50)	t/X^2	P
Gender			0.72	0.473
Male	39 (48.75)	27 (54.00)		
Female	41 (51.25)	23 (46.00)		
Average age (years)	59.56±5.92	60.34±6.15	1.18	0.241
Average body weight (Kg)	65.54±11.03	63.95±10.57	0.81	0.418
Smoking			0.08	0.781
Yes	42 (52.50)	25 (50.00)		
No	38 (47.50)	25 (50.00)		
Drinking			0.44	0.505
Yes	40 (50.00)	28 (56.00)		
No	40 (50.00)	22 (44.00)		
Hyperlipidemia			0.84	0.359
Yes	45 (56.25)	24 (48.00)		
No	35 (43.75)	26 (52.00)		
Hypertension			1.70	0.192
Yes	43 (53.75)	21 (42.00)		
No	37 (46.25)	29 (58.00)		
Diabetes			0.20	0.657
Yes	40 (50.00)	27 (54.00)		
No	40 (50.00)	23 (46.00)		

Protein level of ALDH2: Western blot was used to detect the expression level of ALDH2 protein of serum in the two groups, and ALDH2/GAPDH ratio represented the relative expression level.

Afterwards, the mRNA and protein expression levels of ALDH2 in serum of patients in groups A and B were compared.

(2) Recovery of patients was assessed.

Before treatment, the National Institutes of Health Stroke Scale (NIHSS) score was used to evaluate the neurological function of patients [17]. According to the score, 1-4 points is classified as mild stroke, 5-15 points as moderate stroke and 16 or more as severe stroke. Among them, 30 were mild stroke, 27 were moderate stroke and 23 were severe stroke. Patients were followed up for 3 months after treatment. Barthel index (BI) [18] was used to evaluate their function 3 months after treatment. When BI index was ≥85, they recovered well. An index less than 85 was considered as poor recovery.

(3) Expression level of serum in different stroke patients was analyzed and compared.

After the ALDH2 expression level of stroke patients was detected, the serum ALDH2 expression level of different patients was analyzed according to different conditions. Based on stroke area, ≥4 cm^2 was a large-scale stroke and <4 cm^2 was a small-scale stroke. There were 38 cases of small-scale stroke and 42 cases of large-scale stroke. Concurrently, according to their stroke area, the serum ALDH2 expression level was compared.

Statistical methods

SPSS 19.0 (Asia Analytics Formerly SPSS China) was used for statistical analysis of comprehensive data, and X^2 test was used for the counting data, such as gender, presence or absence of hypertension, hyperlipemia and diabetes. The measurement data were expressed as (X+S), and t test was used, such as comparing mRNA and protein expression levels of ALDH2 in groups A and B. In the meantime, it is necessary to analyze the expression level of ALDH2 mRNA and protein in patients with different pathological characteristics. All variables of prognostic risk factors were selected by SPSS 19.0 software for forward selection, backward selection and finally stepwise regression. Then the risk factors related to prognosis of middle-aged and elderly patients with acute cerebral hemorrhage after minimally invasive surgery were analyzed. First, univariate Logistic regression analysis was used to select important variables, and then multivariate logistic regression model was used to select important independent risk factors. A *p* value lower than 0.05 had statistical significance.

Results

General information table

The age range of 180 middle-aged and elderly patients with acute cerebral hemorrhage treated in Inner Mongolia Forestry General Hospital was 49 to 79 years old, and there was no clear difference in age, hypertension, diabetes and other general data (P>0.05) (**Table 2**).

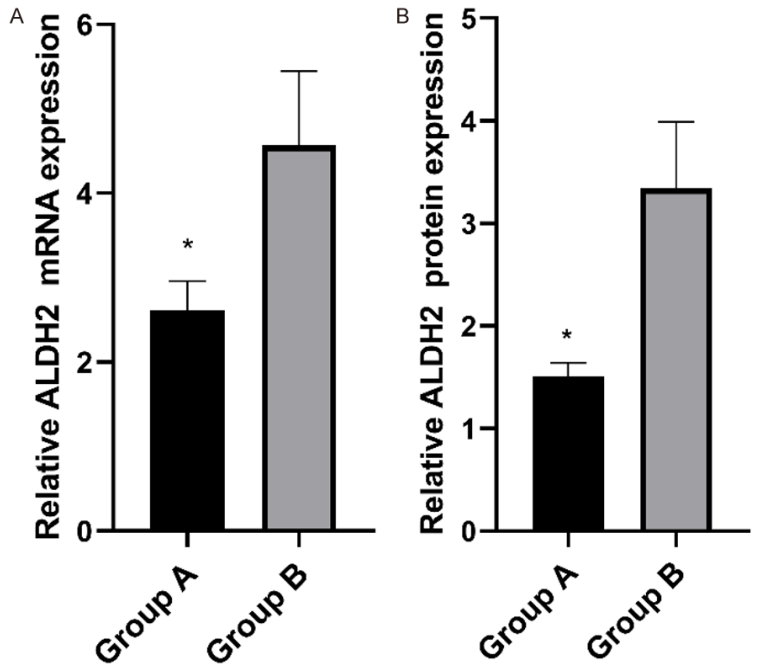

Figure 1. Relative expression level of ALDH2 in serum of groups A and B. A. mRNA relative expression level of ALDH2 in serum of groups A and B: in serum of group A patients after treatment it was dramatically lower than that of group B (P<0.05). B. In the serum of group A patients after treatment it was dramatically lower than that of group B (P<0.05). Note: * indicates comparison with group B (P<0.05).

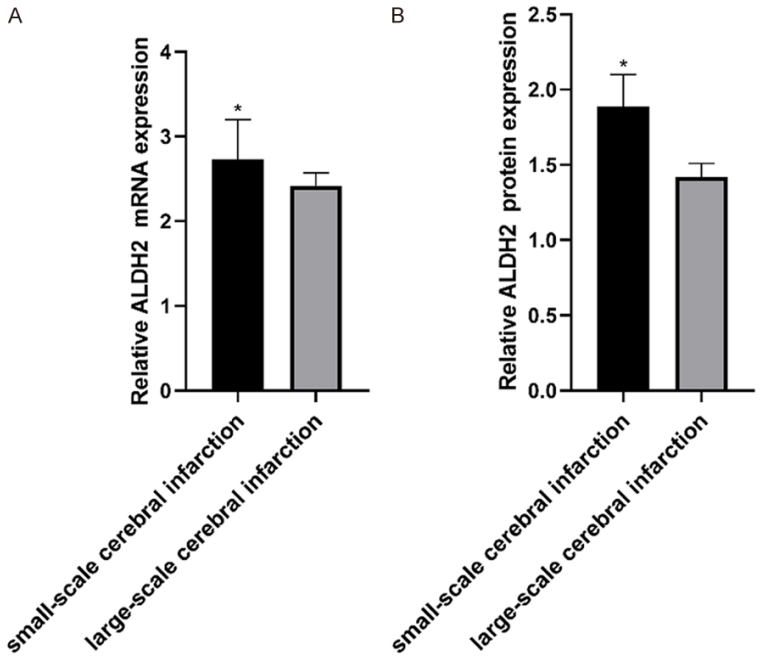

Figure 2. Relative expression level of ALDH2 in patients with different stroke ranges. A. mRNA relative expression level of ALDH2 in patients with different stroke ranges: in serum of patients with small stroke ranges it was higher than that of patients with large stroke ranges (P<0.05). B. Relative protein expression level of ALDH2 in patients with different stroke ranges: in serum of patients with small stroke ranges it was higher than that of patients with large stroke ranges (P<0.05). Note: * indicates comparison with large-scale stroke patients (P<0.05).

Relative expression level of ALDH2 in serum of groups A and B

The relative expression level of ALDH2 mRNA in group A was (2.61±0.35), and that in group B was (4.57±0.88). The relative expression level of ALDH2 protein in group A was (1.51±0.13), and that in group B was (3.34±0.65). Compared between groups, the relative expression level of ALDH2 mRNA and protein in serum of group A patients after treatment was dramatically lower than that of group B (P<0.05) (**Figure 1**).

Relative expression level of ALDH2 in patients with different stroke ranges

The mRNA expression level of ALDH2 in the serum of patients with small-scale stroke was (2.73±0.47) and that of patients with large-scale stroke was (2.42±0.15). The protein expression level of ALDH2 in the serum of patients with small-scale stroke was (1.89±0.21) and that of patients with large-scale stroke was (1.42±0.09). The relative expression level of ALDH2 mRNA and protein in serum of patients with small-scale stroke was higher than that of patients with large-scale stroke (P<0.05) (**Figure 2**).

Relative expression level of ALDH2 in patients with different pathological characteristics

Through the analysis of the relative expression levels of ALDH2 mRNA and protein in pa-

Table 3. Relative expression level of ALDH2 in patients with different pathological characteristics

Clinical parameters	Number of cases	ALDH2 mRNA expression	T	P	ALDH2 protein expression	T	P
Gender			0.80	0.426		1.37	0.175
Male	39	2.60±0.14			1.45±0.12		
Female	41	2.57±0.19			1.49±0.14		
Smoking			0.457	0.651		0.68	0.497
Yes	42	2.71±0.27			1.65±0.21		
No	38	2.68±0.32			1.62±0.18		
Drinking			5.84	<0.001		7.82	<0.001
Yes	40	2.49±0.25			1.50±0.14		
No	40	2.83±0.27			1.72±0.11		
Hyperlipidemia			0.99	0.324		0.59	0.56
Yes	45	2.56±0.11			1.64±0.24		
No	35	2.53±0.16			1.67±0.21		
Hypertension			1.36	0.18		0.58	0.57
Yes	43	2.64±0.14			1.52±0.25		
No	37	2.68±0.12			1.55±0.21		
Diabetes			6.02	<0.001		11.72	<0.001
Yes	40	2.43±0.27			1.50±0.14		
No	40	2.78±0.25			1.83±0.11		

Table 4. Recovery effect of patients and NISS score

Indicators	On admission	Follow-up after 3 months		t/X^2	P
		Good recovery	Poor recovery		
n	80	59	21	100.60	<0.0001
NISS score	7.48±1.07	4.24±0.45	9.56±1.53	302.50	<0.0001

tients with different pathological characteristics, we could conclude that there was no clear difference in the relative expression levels of ALDH2 mRNA and protein among patients with different gender, smoking preference, presence or absence of hypertension and hyperlipidemia (P>0.05), while those in patients with diabetes were markedly lower than those in patients without diabetes, and the relative expression levels of LDH2 mRNA and protein in patients who liked drinking were markedly lower than those who did not like drinking (P<0.05) (**Table 3**).

Recovery effect of patients

We followed up the patients three months after admission. Of those patients, 59 recovered well and 21 recovered poorly. On admission, the average NISS score was (7.48±1.07), while the follow-up results after three months showed that the average score of patients with better recovery was (4.24±0.45), and that of patients with worse recovery was (9.56±1.53), clearly higher than that of patients with better recovery (P<0.05) (**Table 4**).

Relative expression level of ALDH2 in stroke patients with different degrees

The mRNA expression level of ALDH2 in the serum of patients with mild stroke was (2.88±0.42), that of patients with moderate stroke was (2.54±0.32), and that of patients with severe stroke was (2.18±0.11). The protein expression level of ALDH2 in the serum of patients with mild stroke was (1.89±0.21), the mRNA expression level in the serum of patients with moderate stroke was (1.61±0.11) and the protein expression level in the serum of patients with severe stroke was (1.37±0.09). The mRNA and protein levels of serum ALDH2 in patients with moderate and severe cerebral infarction were lower than those in patients with mild stroke, while the mRNA and protein levels of serum ALDH2 in patients with severe cerebral

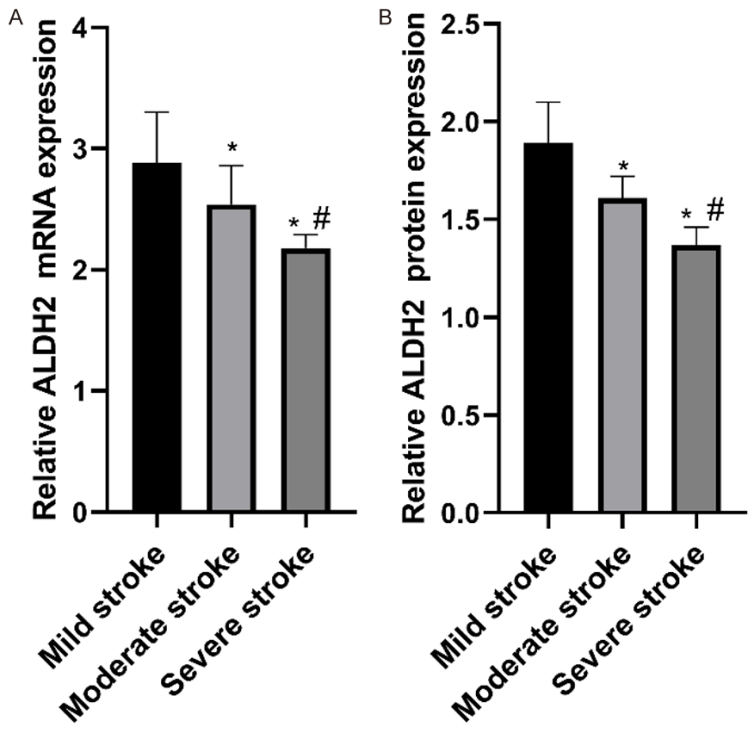

Figure 3. Relative expression level of ALDH2 in different degree of stroke patients. A. Relative mRNA expression level of ALDH2 in stroke patients with different degrees: the ALDH2 mRNA level in serum of patients with moderate and severe cerebral infarction was lower than that of patients with mild stroke, and that of patients with severe cerebral infarction was lower than that of patients with moderate stroke (P<0.05). B. Relative protein expression level of ALDH2 in stroke patients with different degrees: in serum of patients with moderate and severe cerebral infarction it was lower than that of patients with mild stroke, and that of patients with severe cerebral infarction was lower than that of patients with moderate stroke (P< 0.05). Note: * indicates comparison with mild stroke patients (P<0.05), and # indicates comparison with moderate stroke patients (P<0.05).

Table 5. Logistic regression analysis variable assignment

Factor	Variable	Assignment
Gender	X1	Male =1, female =0
Smoking	X2	Yes =1, no =0
Drinking	X3	Yes =1, no =0
Hypertension	X4	Yes =1, no =0
Hyperlipidemia	X5	Yes =1, no =0
Diabetes	X6	Yes =1, no =0
NISS score	X7	Continuous variable
ALDH2	X8	Continuous variable

Table 6. Factors affecting prognosis of stroke

Risk factors	β value	SE value	Wald value	P	OR	95% CI
Diabetes	3.549	2.454	1.892	0.014	2.318	1.784-3.532
Drinking	1.338	0.367	5.240	0.027	1.154	0.679-3.218
NISS score	1.914	0.632	2.781	0.035	1.451	1.024-2.176
ALDH2	1.338	0.367	5.240	0.027	1.154	0.679-3.218

infarction were lower than those in patients with moderate stroke (P<0.05) (**Figure 3**).

Prognostic analysis of risk factors

Multivariate logistic regression analysis displayed that ALDH2 expression level in serum, NISS and diabetes could be used as prognostic factors for acute stroke (**Tables 5**, **6**).

Discussion

The rising disability and fatality rate of acute cerebral infarction [19] and its economic and mental burden on patients [20] make its prevention and treatment of great significance. Recently, some molecules such as MMP-9 have been used as prognostic factors for acute cerebral infarction [21]. It is undoubtedly a good method to use molecules for prognosis of acute cerebral infarction. The purpose of this study is to analyze the ALDH2 expression in serum of patients with AIS, and to verify its clinical and prognostic value.

This experiment first analyzed the relative expression levels of ALDH2 mRNA and protein in serum of patients with AIS and normal physical examination. The results demonstrated that those in patients with acute stroke were lower than those in the serum of normal physical examination subjects. ALDH2 is very momentous in cardiovascular and cerebrovascular diseases such as coronary heart disease. Studies have found that the activation of this factor plays a key part in the protection of ischemic reperfusion of the heart, and its variation and deletion are easy to aggravate cardiovascular and cerebrovascular dis-

eases such as cerebral infarction [22, 23]. From the detection of the relative expression level of ALDH2 mRNA and protein between normal physical examination and acute stroke, this point can be preliminarily obtained.

This experiment also tested the relative expression levels of ALDH2 mRNA and protein in patients under different conditions. The results showed that those in serum of patients with small-scale stroke were higher than those of patients with large-scale stroke. Concurrently, we classified patients into mild, moderate and severe cases according to NISS score. The results manifested that the mRNA and protein contents of ALDH2 in patients with mild, moderate and severe stroke decreased gradually. From here, we can conclude that the ALDH2 relative expression in stroke patients will decrease with the expansion of stroke range and decrease with the increase of severity. This further proves that clinically, the aggravation of cardiovascular diseases is tied to the decrease of ALDH2 [24]. We also detected the relative expression levels of ALDH2 mRNA and protein in patients with different pathological features. The results showed that those were remarkably lower than those in patients without diabetes, and those in patients who liked drinking were remarkably lower than those who did not like drinking. This revealed that drinking had an important influence on ALDH2. This was very similar to the results of Zhang et al. [25]. Alcohol is prone to produce some harmful aldehydes, causing damage to human systems. When ALDH2 is absent, the effect on these aldehydes reduces greatly [26]. According to the results of this study, when ALDH2 is absent, the harmful aldehydes produced by alcohol will further expand the damage to stroke. However, reduction and variation of ALDH2 will also aggravate the severity of diabetes [27]. Hence, if patients suffer from diabetes and stroke at the same time, ALDH2 expression will be lower. This indicates that clinically, ALDH2 expression level will decrease after the severity of the disease and range of stroke are enlarged. ALDH2 expression can be considered for judging the aggravation of the patients' condition clinically. Simultaneously, our experiment also carried out multivariate logistic regression analysis on gender, smoking and drinking. The results showed that ALDH2, drinking, diabetes and NISS score were prognostic risk factors.

There are still shor tcomings in this experiment. We have not been able to test the effect of different treatment methods on ALDH2 expression level. What's more, due to the lack of experimental equipment, we have not been able to test the deeper molecular mechanism of stroke caused by ALDH2 deficiency. In future experiments, we will compare the effects of different treatment methods on ALDH2 level. We will also step up procurement of equipment to try to verify the deeper molecular mechanism.

Overall, decrease and absence of ALDH2 expression level will easily lead to the occurrence, deterioration and area enlargement of AIS. It can be used as a molecular target to judge the severity of symptoms and also as an effective prognostic risk factor clinically.

Disclosure of conflict of interest

None.

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