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ORIGINAL COMMUNICATION

A case–control study of the determinants for cervicocerebral artery dissection

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Abstract

Background Cervicocerebral artery dissection (CAD) is a major cause of ischemic stroke in young adults. There are many existing studies on determinants for CAD; however, they are still not totally defined. We conduct the study to further investigate the determinants for CAD based on ischemic stroke patients.

Methods 81 ischemic stroke patients with CAD were enrolled in the CAD stroke group and 84 ischemic stroke patients without CAD were enrolled in the non-CAD stroke group. Their clinical data, such as age, gender, vascular risk factors, headache and neck pain and clinical laboratory data, were collected to analyze the differences between the two groups.

Results A total of 165 ischemic stroke patients were included. The mean age of CAD stroke group was (51.6 ± 12.4) years, and (55.5 ± 8.1) years in non-CAD stroke group, with a statistically significant difference ($P = 0.017$). The average level of triglycerides in CAD stroke group was (1.3 ± 0.7) mmol/L, and (1.7 ± 1.1) mmol/L in non-CAD stroke group, with a statistically significant difference ($P = 0.012$). There were 42.0% (34/81) of headache and neck pain in CAD stroke group and 22.6% (19/84) in non-CAD stroke group, with a statistically significant difference ($P = 0.008$). The key findings with significant difference were stratified and multivariate logistic regression analysis showed that age < 50 years old (OR 2.98, 95% CI 1.43–6.21, $P = 0.004$), triglycerides < 1.6 mmol/L (OR 3.51, 95% CI 1.69–7.27, $P = 0.001$) and headache and neck pain (OR 2.94, 95% CI 1.39–6.20, $P = 0.005$) showed a positive correlation with CAD.

Conclusion In the process of diagnosis and treatment of ischemic stroke, for patients with age < 50 years old, headache and neck pain and triglycerides < 1.6 mmol/L, the cervicocerebral artery dissection should be considered, and vascular imaging examination needs to be performed in time.

Keywords Cervicocerebral artery dissection · Ischemic stroke · Triglycerides · Headache and neck pain

Introduction

Cervicocerebral artery dissection (CAD) refers to the intramural hematoma caused by the rupture of nutrient arteries in the wall of the cervicocerebral artery, or the blood enters the vessel wall through the damaged and torn arterial intima so that an intramural hematoma is formed between the intima and the media, or an aneurysmal dilation occurs between the media and the adventitia [1]. CAD includes the internal carotid artery dissection (ICD) and the vertebrobasilar artery dissection (VAD). The incidence of CAD in the general population is low, ranging from 2.6/100,000 to 3/100,000 [2]. Because some patients do not show any symptoms or only minor non-specific symptoms (such as headache and neck pain), the true incidence may be higher. Although 1–2.5% of ischemic strokes are due to cervicocerebral artery dissection,

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CAD is a major cause of ischemic stroke in young adults. Epidemiological studies have found that 5–25% of ischemic stroke patients under the age of 45 are caused by artery dissection [3]. However, the etiology of the cervicocerebral artery dissection is not yet totally defined and may be the result of a combination of genetic and environmental factors. Some of the determinants that have been reported include hereditary connective tissue disease, hypertension, migraine, recent infection history, neck trauma and so on. This study aims to further explore the determinants of the cervicocerebral artery dissection through comparing CAD stroke patients with non-CAD stroke patients.

Methods

Study population

81 consecutive CAD ischemic stroke patients diagnosed and treated in the Department of intervention Neurology, the First Affiliated Hospital of Zhengzhou University from 2010 to 2017 and 84 consecutive non-CAD ischemic stroke patients in Department of Neurology were enrolled as the study subjects. All of them were diagnosed by experienced neurological physicians based on cranial imaging and clinical manifestations. Their clinical data was collected prospectively through face-to-face interviews. Patients gave informed consent before participating, and all information that would potentially expose a specific individual patient to identification had been encrypted. The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (Number: KW-2018-LW-006).

Inclusion and exclusion criteria: (1) digital subtraction angiography (DSA) was recognized as the gold standard for CAD, so all CAD patients underwent DSA with one of typical radiological characteristics, such as intimal flap, tail-like occlusion, sign of fire, double lumen, string sign, and pseudoaneurysm-like dilation. Latrogenic dissection after endovascular procedure and monogenic diseases known to cause CAD (e.g., vascular Ehlers–Danlos syndrome) were excluded; (2) for patients in the non-CAD group, no signs related to CAD were found on ultrasound or angiographic examination (CTA, MRA, or DSA) and patients with cardiopathies who had a very high embolic risk were excluded; (3) for patients in two groups, the brain imaging examination (CT or MRI) confirmed that the infarction lesion was located in the blood supply area of the involved artery. Patients with incomplete clinical data were excluded.

Data collection

The age, gender, vascular risk factors, headache and neck pain, and clinical laboratory data were collected for both groups. Vascular risk factors were defined as follows: primary hypertension: systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, or taking antihypertensive drugs; diabetes: fasting blood glucose $\geq$ 7.0 mmol/L, 2 h postprandial $\geq$ 11.1 mmol/L, or undergoing hypoglycemic therapy; low-density lipoprotein(LDL): with a boundary of 1.80 mmol/L which was the secondary prevention standards of ischemic cerebrovascular diseases, it was divided into LDL < 1.80 mmol/L and LDL $\geq$ 1.80 mmol/L. History of smoking/drinking: according to smoking/drinking status, it was divided into three types: no smoking/drinking, past smoking/drinking, and currently smoking/drinking. Recent infection history: infection within 1 month before onset of artery dissection, including respiratory, digestive and other infections. Age, total cholesterol, triglycerides, high-density lipoprotein were compared by quantitative variables.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (mean ± SD), and Student's *t* test was used for statistical difference analysis. Qualitative data were expressed as percentage (%), and Chi square test or Fisher's exact test was used for statistical difference analysis. In the analysis of determinants of the CAD, the above-mentioned features with significant significance were stratified and then collectively included in a multivariate logistic regression analysis. All data were analyzed using SPSS version 22.0, and if $P < 0.05$ the difference was considered statistically significant.

Results

1. Analysis of clinical characteristics of two groups

A total of 165 ischemic stroke patients were included in the study. In CAD group, there are 35 patients with extracranial CAD and 46 patients with intracranial CAD. The mean age in the CAD stroke group was (51.6 ± 12.4) years and (55.5 ± 8.1) years in the non-CAD stroke group, with a significant difference ($P = 0.017$). The average level of triglycerides in the CAD stroke group was (1.3 ± 0.7) mmol/L, and (1.7 ± 1.1) mmol/L in the non-CAD stroke group, with a significant difference ($P = 0.012$). There were 42.0% (34/81) of headache and neck pain in patients with CAD stroke, and 22.6% (19/84) in the non-CAD stroke group, with a significant difference ($P = 0.008$). However, no statistically significant differences were found in gender, hypertension, diabetes, smoking, drinking, low-density lipoprotein, total cholesterol, recent infection history, and high-density lipoprotein between the two groups (Table 1).

2. Analysis of determinants for CAD

Table 1 Comparison of clinical characteristics of the two groups

Clinical characteristics	Total ($n=165$)	CAD stroke ($n=81$)	Non-CAD stroke ($n=84$)	P value
Age (years)	53.5 ± 10.6	51.6 ± 12.4	55.5 ± 8.1	0.017
Male (%)	116 (70.3%)	58 (71.6%)	58 (69.0%)	0.719
Hypertension (%)	98 (59.4%)	48 (59.3%)	50 (59.5%)	0.972
Diabetes (%)	27 (16.4%)	10 (12.3%)	17 (20.2%)	0.171
Past smoking (%)	10 (6.1%)	3 (3.7%)	7 (8.3%)	
Currently smoking (%)	63 (38.2%)	26 (32.1%)	37 (44.1%)	0.328
Past drinking (%)	8 (4.8%)	3 (3.7%)	5 (6.0%)	
Currently drinking (%)	63 (38.2%)	26 (32.1%)	37 (44.0%)	0.180
LDL ≥ 1.80 (mmol/L)	125 (75.8%)	58 (71.6%)	67 (79.8%)	0.222
Triglycerides (mmol/L)	1.49 ± 0.91	1.31 ± 0.66	1.66 ± 1.07	0.012
Total cholesterol (mmol/L)	4.03 ± 1.15	3.88 ± 1.14	4.18 ± 1.15	0.096
HDL (mmol/L)	1.12 ± 0.34	1.15 ± 0.39	1.10 ± 0.28	0.301
Recent infection	16 (9.7%)	10 (12.3%)	6 (7.1%)	0.259
Head and neck pain	53 (32.1%)	34 (42.0%)	19 (22.6%)	0.008

To analyze determinants for CAD, the key findings with significant difference in Table 1 were stratified and then included in multivariate logistic regression analysis. The results showed that age < 50 years old (OR 2.98, 95% CI 1.43–6.21, $P=0.004$), triglycerides < 1.6 mmol/L (OR 3.51, 95% CI 1.69–7.27, $P=0.001$) and headache and neck pain (OR 2.94, 95% CI 1.39–6.20, $P=0.005$) were positively correlated with CAD (Table 2).

Discussion

With the development and popularization of vascular imaging techniques such as CTA/MRA and DSA in recent years, neurological physicians have become increasingly aware of the cervicocerebral artery dissection and CAD is no longer a rare cerebrovascular disease. Debette et al. revealed that patients with CAD usually lacked the common risk factors of cerebrovascular disease by comparing 690 ischemic stroke patients with CAD and without CAD [4]. However, among young and middle-aged ischemic stroke patients younger than 45 years old, 5–25% are due to artery dissection. As we all know, CAD has become the second cause of ischemic stroke in young and middle-aged adults [5]. Combining color Doppler ultrasound, MRI and MRA, Morel A et al performed a retrospective analysis involving 172 patients with dissection and clarified the mechanism of ischemic stroke in cervical artery dissection patients [6]. The results showed that the majority (85%) of ischemic stroke patients were because of thromboembolism, a small part (12%) because of hemodynamics, and the rest because of the combined effects of the above two mechanisms.

CAD can occur at any age, most commonly between 35 and 50 years old. In this study, the mean age of CAD stroke group was 51 years, which was higher than that of the study of 301 Finnish CAD patients [7]. However, it was roughly consistent with epidemiological peak age of CAD. Compared with the non-CAD stroke patients, the mean age of CAD stroke patients was younger. There was also a statistically significant difference in multivariate regression analysis, indicating that age < 50 years old was a risk factor for CAD. Engelter et al. found that younger patients were more likely to have a minor trauma, by which the mean age of CAD patients was younger [8]. It suggested that in young and middle-aged patients with cerebral infarction, it was necessary to consider the artery dissection in the course of medical treatment, and DSA should be underwent to confirm the diagnosis timely.

In recent years, an international, large-scale, multicenter study performing research on cervical artery dissection and

Table 2 Analysis of determinants of CAD

Clinical characteristics	CAD stroke ($n=81$)	Non-CAD stroke ($n=84$)	P univariate	OR (95% CI)	P value
Age < 50 years old	35 (43.2%)	18 (21.4%)	0.003	2.98 (1.43–6.21)	0.004
Triglyceride < 1.6 mmol/L	60 (74.1%)	44 (52.4%)	0.004	3.51 (1.69–7.27)	0.001
Head and neck pain	34 (42.0%)	19 (22.6%)	0.008	2.94 (1.39–6.20)	0.005

ischemic stroke patients (CADISP) included 690 cervical artery dissection, 556 non-CAD ischemic strokes, and 1170 healthy controls from France, Belgium, Finland, and Italy, and compared the vascular risk factors among the groups. The results showed that the proportion of hypercholesterolemia in patients with cervical artery dissection was lower than the rest two groups, and the difference was statistically significant [4]. As the serum cholesterol level increases, so does the risk of atherosclerosis. The negative correlation between cholesterol level and cervical artery dissection may be due to migration and proliferation of media smooth muscle cells, increased synthesis of extracellular matrix, decreased catabolism, and increased cross-linking of collagen and elastin, which made the artery wall to become more stiffer and less prone to tear [9]. For the blood lipids involved in this study, the average total cholesterol level in the CAD stroke patients was higher than that in the non-CAD stroke patients, but there was no significant difference in statistical analysis. However, triglycerides < 1.6 mmol/L between two groups was statistically significant in multivariate logistic regression analysis. The previous studies on atherosclerosis mostly focused on plasma cholesterol level. More and more epidemiological studies and molecular mechanisms have shown that elevated plasma triglycerides level is also one of independent risk factors for atherosclerosis [10]. Therefore, we speculated that triglycerides also reduced the occurrence of artery dissection by promoting the formation of atherosclerosis. At the same time, the elevation of triglyceride will also lead to the accumulation of adipose tissue in the body, thus buffering minor trauma and reducing the chance of CAD.

In CAD stroke patients, approximately 30% of internal carotid artery dissections and 50–60% of vertebral artery dissection patients had headache and neck pain [11]. The proportion of patients with headache and neck pain in the CAD ischemic stroke group in this study was consistent with the above results. Compared with the non-CAD stroke group, there was a significant difference in multivariate logistic regression analysis, indicating that headache and neck pain was positively correlated with CAD. According to reports, there were abundant nerves wrapping around the arteries, and tearing of the artery wall was the direct reason of headache and neck pain [12]. In addition, local pain-sensitive structures around the CAD aneurysm can also cause headache and neck pain when pulled. Therefore, in the face of ischemic stroke patients with headache and neck pain, we should be alert to the possibility of artery dissection.

In CAD stroke group, there were more males than females. However, no statistically significant difference was found compared with non-CAD stroke group. Recent infections had been shown to be related to the artery dissection in previous studies [13, 14]. In this study, the proportion of patients with a history of recent infection in the CAD stroke group was higher than that in the non-CAD stroke group. However, there was no significant difference between the two groups. Although hypertension has been considered as one of the independent risk factors for aortic dissection [15], its relationship with CAD remains controversial. In this study, the proportion of hypertensive patients in the two groups differed little, and there was no significant difference in statistical analysis. Two case–control studies from France and Italy shown that hypertension was not related to the occurrence of artery dissection [16, 17], similar to the results of this study. However, in the CADISP study, comparing 690 cervical artery dissection patients with 1170 healthy controls, the proportion of hypertension in the cervical artery dissection group was higher. It is suggested that hypertension is related to the occurrence of cervical artery dissection [4]. The sample content in this study was relatively small compared with CADISP, and the healthy control group was not set. Therefore, it is necessary to further increase the sample content to reduce the bias and verify the relationship between the artery dissection and hypertension.

In addition to the factors mentioned above, studies on determinants of CAD in foreign countries still found that history of migraine, especially aura migraine [18], and minor trauma in the first 3 weeks preceding the artery dissection have a positive correlation with the CAD [19], and CAD is more frequent in the autumn and winter cold season [20]. Due to the absence of some case data and the relatively small sample size in this study, blind inclusion will result in serious bias, therefore the study did not involve the above-mentioned determinants. However, compared with previous studies, all cases in this study were ischemic stroke patients, which enhanced the comparability of the case group and the control group, and effectively controlled the confounders. In addition, we included 81 cases in the CAD stroke and 84 cases in the non-CAD stroke group, respectively, and the ratio was close to 1:1, which improved the efficacy of the study. Our study included some limitations as follows. The number of our cases was limited. There would be recall bias in history of recent infection in the previous weeks. Moreover, all patients were enrolled from the first affiliated hospital of Zhengzhou University, a tertiary teaching hospital, which could result in admission rate bias.

Conclusion

In the process of clinical diagnosis and treatment of ischemic stroke patients, for patients with age < 50 years old, headache and neck pain and triglycerides < 1.6 mmol/L, the cervicocerebral artery dissection should be considered, and vascular imaging examination needs to be improved in time. We should attach great importance to the timely investigation of CAD, if necessary, interventional treatment should be

performed to avoid omissions and to prevent the development of the disease and the occurrence of adverse outcomes such as hemorrhagic stroke.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethics approval All subjects gave their informed consent prior to their inclusion in the study. The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (Number: KW-2018-LW-006).

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