

Predictors of Ischemic Events Secondary to Cervicocerebral Artery Dissection

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Abstract

Objective : To identify the predictors of ischemic events secondary to cervicocerebral artery dissection (CAD). **Methods :** Consecutive patients with cervicocerebral artery dissection from 2010 to 2017 were registered as study subjects, who were classified as patients with and without ischemic events. Clinical data were collected prospectively, such as demographics, vascular risk factors, headache and neck pain, dissection site and laboratory test. A case-control study was performed to compare the clinical data between two groups. **Results :** A total of 130 patients with cervicocerebral artery dissection were included, in which 70.0% (91/130) suffered from ischemic events, including 81 ischemic strokes and 10 transient ischemic attacks. There were 46.2% (42/91) and 25.6% (10/39) of the artery dissections located in the anterior circulation in the CAD patients with and without ischemic events respectively ($p = 0.029$). The average level of HDL was (1.14 ± 0.38) mmol/L in the CAD patients with ischemic events, and (1.28 ± 0.48) mmol/L in the CAD patients without ischemic events ($p = 0.083$). Multivariate logistic regression analysis showed that there was a positive correlation between anterior circulation and ischemic events (OR=3.204, 95% CI 1.305-7.863, $p = 0.011$) and HDL level was negatively correlated with ischemic events (OR=0.335, 95% CI 0.130-0.867, $p = 0.024$) in CAD patients. **Conclusion :** Ischemic events are common complications of cerebrovascular disease in CAD patients, especially for those with an artery dissection located in the anterior circulation and low serum HDL level. **Key Word :** cervicocerebral artery dissection, ischemic event, HDL, anterior circulation, predictor

Background

Cervicocerebral artery dissection (CAD) occurs when the blood enters the vessel wall through the damaged and torn intima or the rupture of the vaso vasorum happens in the media, leading to an intramural hematoma between the intima and the media or an aneurysmal dilation between the media and the adventitia [1,2]. The clinical presentation of CAD is higher variable, including ischemia, local signs and symptoms, or both. With the rapid development of neuroimaging technology, more and more ischemic events secondary to CAD are well known. Although only about 2% of all ischemic strokes are due to cervicocerebral artery dissection, CAD is one of the major causes of ischemic stroke in young and middle-aged patients, accounting for 5% to 25% of patients with ischemic stroke below the age of 45 [3]. And recurrent ischemic events are significantly more frequent in patients with ischemic events at onset than in patients with local symptoms or asymptomatic patients [4]. Therefore, it is particularly important in CAD patients to timely assess the risk of secondary ischemic events and actively improve risk factors so as to prevent the occurrence of ischemic events. However, it is unclear whether CAD patients with and without ischemic events differ in demographic characteristics, the prevalence of vascular risk factors and local symptoms. Thus, we conducted a case-control study to identify the predictors of ischemic events in cervicocerebral artery dissection patients.

Methods

1. Study population

The methods had been established and described in detail previously [5]. Consecutive patients with cervicocerebral artery dissection treated in the Interventional Neurology Department of the First Affiliated Hospital of Zhengzhou University from 2010 to 2017 were prospectively registered as study subjects, who were categorized into patients with and without ischemic events. According to the duration of ischemic deficits, ischemic event included ischemic stroke (>24 hours) and TIA (≤ 24 hours). CAD patients were diagnosed by experienced neurologists on the basis of vascular imaging and clinical manifestations. All patients were given informed consent before participating and signed the consent after full understanding.

Patients were included in the study if they had one of the characteristic signs of artery dissection on digital subtraction angiography (DSA), such as signs of fire, tail-like occlusion, string sign, or pseudoaneurysm-like dilation, known as the gold standard for diagnosis of CAD [6]. And most patients underwent CTA and/or MRA prior to DSA (FIGURE 1); and for patients with ischemic events, if the brain imaging and vascular imaging examination confirmed that the responsible focuses leading to ischemic stroke were located in the blood supply area of the dissected artery and the symptoms of focal brain dysfunction attributed to TIA were consistent with the ischemic manifestations of blood supply area of the dissected artery. Similarly, patients were excluded if the CAD had a clear cause, such as iatrogenic, head and neck trauma, muscle fiber dysplasia; if CAD patients had concurrent subarachnoid hemorrhage; and if CAD patients had incomplete clinical data; and for patients with ischemic events, if there were potential causes of ischemic events other than CAD, such as hypercoagulability, hematological diseases, atrial fibrillation, arteritis.

2. Data collection

The clinical data on demographics, vascular risk factors, headache and neck pain, dissection site and laboratory test were collected through face-to-face interviews. The demographics included age and gender. We defined vascular risk factors as follows: hypertension defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive drugs; diabetes mellitus defined as fasting venous plasma glucose concentration ≥ 7.0 mmol/L, 2 hours postprandial plasma glucose concentration ≥ 11.1 mmol / L, or use of hypoglycemic drugs; history of smoking/drinking classified as no smoking/drinking and smoking/drinking according to current smoking/drinking status; recent infection history defined as infection within 1 month prior to the onset of cervicocerebral artery dissection, consist of respiratory infection and digestive infection. The clinical data on laboratory test included total cholesterol, triglycerides, high-density lipoprotein (HDL), low density lipoprotein (LDL), of which low-density lipoprotein was divided into $LDL < 1.80$ mmol/L and $LDL \geq 1.80$ mmol/L with a boundary of 1.80 mmol/L, the secondary prevention standard of ischemic cerebrovascular disease. The dissection site included anterior circulation and posterior circulation.

3. Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (mean \pm SD) and categorical variables were expressed as percentage (%). Differences between CAD patients with and without

ischemic events were analysed using Student's t test, Chi-square test or Fisher's exact test when appropriate. Then, multivariate logistic regression analysis, including above variables with a $p < 0.1$, was performed in order to identify the predictors of ischemic events secondary to cervicocerebral artery dissection. Statistical analysis was carried out using SPSS version 22.0. A two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 130 patients with cervicocerebral artery dissection were included in the present study. The mean age was 50.90 ± 12.85 years and 95 (73.1%) patients were men. Among 130 patients, 91 (70.0%) patients sustained ischemic events causing 81 ischemic strokes and 10 transient ischemic attacks, and 39 (30.0%) patients presented with local symptoms or signs, including headache and neck pain, homonymous hemianopia, and cranial nerve palsy. Demographics and clinical characteristics are shown in table 1.

1. Differences in demographics and clinical characteristics between two groups

Fourty six point two percent (42/91) and 25.6% (10/39) of the artery dissections were located in the anterior circulation in the CAD patients with and without ischemic events respectively ($p=0.029$). The average level of HDL was (1.14 ± 0.38) mmol/L in the CAD patients with ischemic events and (1.28 ± 0.48) mmol/L in the CAD patients without ischemic events ($p=0.083$). However, there were no significant differences were found in age, gender, hypertension, diabetes mellitus, smoking, drinking, LDL, total cholesterol, recent infection, and headache and neck pain. (Table 1)

2. Predictors for ischemic events secondary to CAD

The dissection site and HDL level were included in multivariate logistic regression analysis and remained significant. The results displayed that in CAD patients there was a positive correlation between anterior circulation and ischemic events (OR=3.204, 95% CI 1.305-7.863, $p=0.011$). Conversely, HDL level was negatively correlated with ischemic events (OR=0.335, 95% CI 0.130-0.867, $p=0.024$). (Table 2)

Discussion

The application and development of imaging play a crucial role in the study of the mechanism of ischemic stroke in CAD patients. The stenosis or occlusion of the lumen caused by the arterial dissection could result in hemodynamic disturbance and the hypoperfusion in the corresponding blood supply area would lead to cerebral ischemia in the end. However, the fact that the formation of thrombus secondary to the damaged artery endothelium caused thromboembolism by the detachment of thrombus fragments is the major mechanism of cerebral infarction [7-8]. Oliveira et al [9] demonstrated that high intensity transient signals (HITS) known as microembolic signals, were frequently seen downstream of dissected arteries in patients with CAD by transcranial Doppler sonography (TCD) monitoring, supporting that artery to artery embolism was an important mechanism of ischemic stroke in CAD patients. In a small sample study [10], HITS were found not only in the middle but also in the posterior cerebral artery. In addition, the

type of cerebral infarction shown by neuroimaging of CAD patients also supported microembolism as the main mechanism of stroke. The CT or T2-weighted imaging examination of extracranial internal carotid artery dissection patients with ischemic stroke found that the majority of them were cortical infarctions, large subcortical infarctions, or mixed cortical-subcortical infarctions, and the prevalence of infarctions in the border zone, which is closely related to hemodynamic disorders, was only 3% to 16%. Audrey Morel et al [11] conducted a retrospective study to identify the most likely mechanism of stroke combining the cerebrovascular ultrasound, stroke brain MRI, and cervical MRA. Of 172 consecutive cervical artery dissection patients, 100 patients had acute ischemic stroke on DWI, which was attributed to a thromboembolic mechanism in 85 patients, a hemodynamic mechanism in 12 patients and a mixed mechanism in the remaining patients. And there were no differences between anterior and posterior circulation stroke in the proportion of embolic and hemodynamic stroke.

Cervicocerebral artery dissection mainly cause ischemic events. In the present study, 80.8% (42/52) of artery dissection in the anterior circulation and 62.8% (49/78) of artery dissection in the posterior circulation presented with ischemic events, and there was a significant difference in dissection site, in contrast with the previous studies [12-13], in which they speculated that artery dissections in the posterior circulation could more frequently be subintimal, expanding toward the arterial lumen, thus resulting in a higher prevalence of ischemic stroke, while artery dissections in the anterior circulation could more frequently be subadventitial, expanding externally, leading to aneurysmal dilatations, which were more likely to rupture followed by subarachnoid hemorrhage (SAH). Consistent with our study, the prior report from Taiwan found that ischemia was the predominant presentation of anterior circulation artery dissection [14]. One could hypothesize that it could be ascribed to ethnic difference so that Chinese patients with CAD carry unique clinical characteristics different from western counterparts. Hence CAD patients located in the anterior circulation may be at increased risk for ischemic events and should be paid more attention on in order to prevent the poor outcome. Furthermore, our findings still should be reconfirmed through a national, multicenter, consecutive, prospective cohort study from China in the near future [1].

High-density lipoprotein is recognized as the "scavengers" of blood vessels. The most important function is to reversely transport cholesterol from the peripheral tissues and cells to the liver and then convert it into bile acids or remove it directly from the intestines through bile. Rohatgi et al [15] demonstrated a negative correlation between the inverse cholesterol transport function of HDL and the risk of atherosclerotic cardiovascular disease through a population-based cohort study. Patients with severe stenosis or complete occlusion of the internal carotid dissection artery are more likely to have cerebral ischemic symptoms [16], whereas patients with mild stenosis or non-stenosis have more local signs and symptoms. The results of this study showed that high-density lipoprotein level in CAD patients were inversely related to the occurrence of ischemic event. We hypothesized that HDL reduced the degree of stenosis in the lumen of dissected artery by exerting its function of anti-atherosclerosis, thereby alleviating hypoperfusion in the blood supply area of the brain. In addition, HDL had a protective effect on vascular endothelial cells [17-19], and serum HDL level was negatively correlated with platelet activity in the human body [20], and HDL had anticoagulant function as well. Therefore, HDL could reduce the

formation of local thrombus in the dissected artery through the above-mentioned complex mechanisms, thus preventing the occurrence of ischemic stroke due to artery to artery embolism.

An observational study [16] suggested that hypercholesterolemia occurred more often in internal carotid artery dissection with than without ischemic events, which may result in endothelial dysfunction and then enhance thrombus formation. Although hypertension is an independent risk factor for stroke, it is undefined whether CAD patients with hypertension have a high risk for stroke. A case-control study from Italy discovered that hypertension had a more pronounced effect on cervical artery dissection patients with cerebral infarction as opposed to others without [21]. But in the present study, we observed no significant association between ischemic events and hypercholesterolemia or hypertension. In consequence, further prospective population-based studies are necessary to explore the predictors of ischemic events in CAD patients.

This study had several limitations as follows. The number of our cases was limited. There would be recall bias in history of recent infection in the previous week. All patients were enrolled from the first affiliated hospital of Zhengzhou University, a tertiary teaching hospital, with an underlying referral bias. Moreover, CAD patients with mild local symptoms may not seek medical attention, which was likely to increase the proportion of CAD patients with ischemic events.

Conclusions

In conclusion, our findings suggest that ischemic events are common complications of cerebrovascular disease in CAD patients, especially for those with an artery dissection located in the anterior circulation and low serum HDL level.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Number: KW-2018-LW-006).

Consent to publish

All authors agree to the publication of the final version.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors were involved in the study conception and design, acquisition of data, and analysis and interpretation of data; drafted and revised the manuscript for intellectual content; approved the final version to be published; agree to be accountable for all aspects of the work.

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Tables

Table 1. Differences in demographics and clinical characteristics between two groups

Clinical data	Total (n=130)	CAD with Ischemic Event (n=91)	CAD without Ischemic Event (n=39)	<i>P</i> value
Male, n (%)	95 (73.1)	66 (72.5)	29 (74.4)	0.829
Age, mean ± SD, y	50.90±12.85	50.96±12.17	50.77±14.48	0.940
Smoking, n (%)	55 (42.3)	42 (46.2)	13 (33.3)	0.175
Drinking, n (%)	43 (33.1)	33 (36.3)	10 (25.6)	0.238
Diabetes mellitus, n (%)	15 (11.5)	10 (11.0)	5 (12.8)	0.765
Hypertension, n (%)	73 (56.2)	53 (58.2)	20 (51.3)	0.464
LDL≥1.80mmol/L, n (%)	97 (74.6)	66 (72.5)	31 (79.5)	0.403
Total cholesterol, mean ± SD, mmol/L	3.92±1.06	3.84±1.11	4.10±0.91	0.208
Triglyceride mean ± SD, mmol/L	1.28±0.61	1.29±0.64	1.26±0.54	0.804
HDL mean ± SD, mmol/L	1.18±0.41	1.14±0.38	1.28±0.48	0.083
Anterior circulation, n (%)	52 (40.0)	42 (46.2)	10 (25.6)	0.029
Recent infection, n (%)	18 (13.8)	11 (12.1)	7 (17.9)	0.375
Headache and neck pain, n (%)	56 (43.1)	36 (39.6)	20 (51.3)	0.216

Table 2. Predictors for ischemic events secondary to CAD

Clinical characteristics	OR	OR (95%CI)	<i>P</i> value
Anterior circulation	3.204	1.305~7.863	0.011
HDL	0.335	0.130~0.867	0.024

Figures

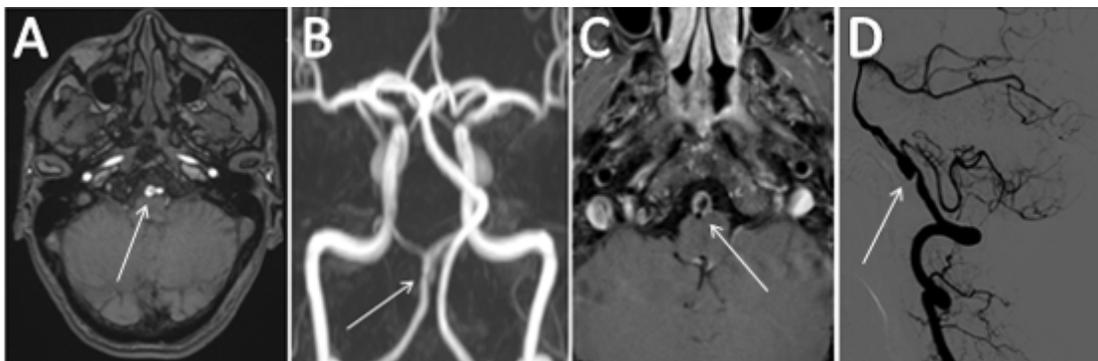


Figure 1

A male patient, 43-year-old, presented with continuous, severe, pulsating pain in the occipital region. (A,B) 3D time-of-flight magnetic resonance angiography (TOF-MRA) revealed a dilated and tortuous vertebral artery and basilar artery (arrow). (C) The contrast-enhanced MRI revealed ring-enhancing right vertebral arterial wall (arrow). (D) Digital subtraction angiography (DSA) revealed a stenosis and aneurysmal dilatation of the right vertebral artery (arrow).