

Identification of risk factors associated with developing ocular ischemia syndrome in patients with carotid artery occlusion

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Abstract

Purpose This study aims to explore risk factors associated with ocular ischemia syndrome (OIS) in patients with late stage carotid artery occlusion (CAO). **Methods** Eighty-seven patients with CAO were enrolled and examined via patient history questionnaire, carotid duplex ultrasonography, transcranial doppler sonography (TCD) and eye examination (slit lamp, ophthalmoscopes). **Results** Twenty-two patients were diagnosed with OIS. Female patients are more likely to development OIS (OR=2.78). Patients without collateral circulation were associated with risk of OIS (OR=4.245, P<0.05). **Conclusions** One quarter of patients with CAO patients had OIS and sex and non-collateral circulation building were associated with OIS.

Background

Carotid artery occlusion (CAO) is one of the leading causes of ischemic stroke. In 46% of cases, ischemic lesions of the eyes will develop subsequently [1,2]. Acute ocular ischemia develops in a majority of cases with ischemic eye lesions. Symptoms include sudden monocular blindness caused by entrapment of emboli in the retina arterial tree [3]. The chronic form of ocular ischemia, also known as ocular ischemia syndrome (OIS), is less common. Reported frequencies range between 5%-21% in patients with carotid artery stenosis or occlusion [4]. The chronic form is explained by a chronic low perfusion pressure that causes diffuse retinal ischemia, reflected by an increase in circulation time, which initially results in dilatation, irregularity of caliber, and tortuosity of retina vessels [5]. In ophthalmoscopy midperipheral microaneurysms, small dot-and-blot intra-retinal hemorrhages, or nerve fiber layer splinter hemorrhages may be observed. The OIS course is long and insidious, but it results severe and irreversible vision loss.

However, it is still unclear why only a subset of CAO patients suffer from OIS. It remains unclear whether or not any clinical or demographic factors are associated with the risk of developing OIS in patients with CAO. Therefore, we aim to identify risk factors which if present, a patient might be more likely to develop OIS. In our clinical work, we found female CAO patients without brain collateral circulation is more prone to develop OIS, so we choose sex and collateral circulation as the tested risk factors. Besides, we hypothesized that these risk factors of CAO [6] could also be risk factors of developing OIS. These risk factors could help ophthalmologists to develop better treatment and management strategy of early OIS.

Methods

Patients enrolled in this study were diagnosed with CAO using carotid duplex ultrasonography between March 1, 2007 and December 31, 2017. CAO was diagnosed with OIS.

Medical and life style survey: Patients were interviewed for their symptoms and vascular risk factors, including hypertension, diabetes, hyperlipidemia, smoking status, alcohol consumption, *etc.* Smoking status is defined by one or more cigarettes per day for at least one year. Alcohol consumption is defined by taking 50g alcohol or more per day for at least one year.

Identification of CAO via carotid duplex ultrasonography: High frequency duplex ultrasonography, CDI and spectral Doppler analysis, and 3D-mode and 4D real-time sonography were used. We evaluated the possibility of vessels (passable, occlusive), the direction of pathway of the vessels (deformity, pathological curling); the pathological changes inside of vessel (arteriosclerotic plaque, its size and structure).

Identification of collateral circulation building via transcranial doppler (TCD): TCD investigations were performed with a multi-Dop X device (TCD inspector, German SciMed). Pulsed Doppler probes (2 MHz) were used for cerebral vessels, and a 4-Mhz probe was used to detect the blood flow of the supratrochlear artery. Because Due to the superficial location of the supratrochlear artery, it is used to detect the condition of homolateral ocular artery blood flow, and therefore indication of collateral circulation building. (Fig. 1)

All patients underwent a standardized ophthalmologic investigation, including measurement of visual acuity and intraocular pressure, slit lamp examination, and fundoscopy in mydriasis on presence of retinal signs; mid-peripheral microaneurysms; multiple small dot-and-blot intraretinal hemorrhages or nerve fiber layer splinter hemorrhages; or dilatation, irregularity of caliber, or tortuosity of veins. Signs of more advanced chronic ocular ischemia were neovascularization of the optic disc, retina or iris (rubeosis iridis), with or without uveitis, or neovascular glaucoma in the absence of any other cause.

Criteria for diagnosis of standard Ocular ischemia Syndrome^[5,8]: 1. carotid stenosis higher than 50%; 2. Amaurosis fugax, impaired vision, ophthalmodynia or orbital pain; 3. Distinctive change of fundus ischemia: petechial hemorrhage at the periphery, venous distention without tortuosity and artery thinness; 4. FFA: the extension of circulation period, defiled attachment of the vessel wall, microangioma and non-perfusion area.

Statistical analysis included the student's t-test, chi-square test and logistic regression. Demographic and risk factors were coded as binary predictor variables, with present as 1 and non-present as 0. P values of <0.05 were considered significant.

Result

It is reported^[6] that age, sex, hypertension, diabetes, hyperlipidemia, smoking, drinking and collateral circulation are potential risk factors of ischemia stroke CAO. Therefore, we hypothesed that these risk factors of CAO could also be risk factors of developing OIS. Thus we selected these factors in this analysis (Table 1).

A total of 87 patients were enrolled in this study and all diagnosed with CAO. 3 of them had bilateral CAO.

To illustrate how collateral circulations were diagnosed, here are two examples of patient cases.

Patient 1 presented with a reduced visual acuity of 0.2. Carotid duplex ultrasonography and TCD revealed a profound stenosis of the left internal carotid artery with little blood flow inside left ocular artery.(Fig2a) Clinical examination revealed rubeosisiridis and dilated retinal veins. In fluorescein angiography peripheral retinal ischemia could be observed. (Fig2b, 2c) A progression of loss of visual acuity to complete visual loss was observed in this patient

Patient 2 presented with a reduced visual acuity of 0.8. Carotid duplex ultrasonography and TCD revealed a profound stenosis of the right internal carotid artery with regurgitant blood flow inside right ocular artery.(Fig3a,3b) Clinical examination revealed mild to moderate retinal ischemia with lighter optic disc and peripheral cotton spots. (Fig.3c). Only mild visual loss was observed in this patient.

Age

22 out of 87 patients were diagnosed with ocular ischemia syndrome (OIS) and 65 patients were not. Patients with OIS are 62.7 years old on average (SD=9.0), and patients without OIS are 69.7 years old on average (SD = 10.3). The age distribution of the patient with OIS and without OIS were not statistically different (T test, P=0.997).

Univariate analysis of risk factors of OIS were performed via simple logistic regression of each factors. Among all the factors, female sex and collateral circulation buildingof ocular artery were statistically different between patients with OIS and patients without OIS (P<0.05).Other factors including hypertension, diabetes, hyperlipidemia, smoking and drinking were not statistically significant. (Table 1). A total of 11 out of 23 female patients developed OIS (47.8%) compared with 11 out of 64 male patients (17.2%), with an odds ratio of 2.78 (P=0.0031). A total of 15 out of 36 patients (41.7%) with no collateral circulation openingdeveloped OIS, compared to 7 out of 44 patients (15.9%) with collateral circulation opening (odds ratio = 4.49, P=0.0037).

Multiple logistic Regression Analysis

Simple logistic regression analysis identified female sex and collateral circulation as potential risk factors associated with OIS. We next investigated whether or not female sex and collateral circulation are independent factors via multiple logistic regression analysis.

In the 87 patients, sex is the negative factor to ocular ischemia and collateral circulation is the positive factor to ocular ischemia. (Table2)

Discussion

Ocular ischemic symptoms are sometimes observed among patients with CAO and some of them may eventually developed to be suffering from OIS with the ocular signs: dilatation, irregularity of caliber, and tortuosity of retinal veins.^[7-9] and midperipheral microaneurysms, small dot-and-blot intraretinal hemorrhages, or nerve fiber layer splinter hemorrhages^[5,9] in retinas. The retina change is explained by a

chronic low perfusion pressure that caused diffuse retina ischemia, reflected by an increase in circulation time. Ischemia is asymptomatic in the early phase. Progression of the disease, however, may lead to OIS with both ocular anterior posterior ischemia finally. While, the existing question is why only some patients with CAO develop OIS.

This study demonstrates that female patients and collateral circulation building are associated with risk of OIS developing in CAO patients. There is a theory that in some CAO patients, collateral blood flow via branches of the external carotid artery may result in reversal of flow in the ophthalmic artery (OphthA) to sustain cerebral blood flow, compensating eye blood flow as well.^[10] If this compensating mechanism plays a role, we might expect it works more frequently in patients of CAO for blood compensation. Our result is also consistent with this hypothesis. Some research^[10] indicates that the common opening arteries in Chinese people were anterior communicating artery (58.8%), posterior communicating artery (47.1%), ocular artery (45.1%). Some research^[10,11] even assumed that venous stasis retinopathy, a common ocular ischemic symptom, is an indicator of impaired blood flow condition of brain and somehow associated with cerebral collateral vessel opening, which seems sensible, but, still needs more confirmation.

In most studies, male are more likely to develop CAO with other brain and heart diseases. However, we saw female are more likely to develop OIS if diagnosed with CAO. This will be extremely helpful for clinicians to allocate resources for better prognosis of CAO if female. We hypothesize that female might be more sensitive and concerned about their vision change and go to see the doctor even if the change is subtle, or perhaps some other substantial mechanism needs to be found out.

Senility, hypertension, diabetes, hyperlipidemia, smoking and drinking were reported^[12] to be associated with risk of CAO. However, in this study, we demonstrate that they are not significantly associated with risk of OIS.

Conclusion

One quarter of patients with CAO patients had OIS and sex and non-collateral circulation building were associated with OIS. Therefore, we recommend that patients with CAO, especially having no collateral circulation, should be referred to the ophthalmologist on routine basis, regardless of whether they have had visual symptoms, for prevention of OIS prevention^[13]. If ischemic symptoms or signs occur, treatment should be started in early stage^[14,15], though a management strategy can not be referred from this study.

Abbreviations

CAO: carotid artery occlusion

OIS: ocular ischemia syndrome

CDI☒color Doppler flow imaging

TCD: transcranial doppler sonography

FFA☒fluorescein fundus angiography

Declarations

Ethics approval and consent to participate

This is a simply Clinical retrospective review without any intervention. It has been approved and consented by local ethic committee, Fujian Provincial Hospital Ethic Community.

Raw data is available in Database of Fujian Provincial Hospital, CN.

Consent for publication

No applicable.

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Contributions:

Conception and design☒MH Huang, S Huang☒

Administrative support☒YZ Wu, S Huang

Provision of study materials and patients☒N Han, ZH Gao

Collection and assembly of data☒MH Huang

Data analysis and interpretation☒ MH Huang , ZH Gao,N han

Manuscript writing☒All authors

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Tables

Table 1 Univariate analysis of ocular ischemia related to carotid stenosis

		Ischemia group	Non-ischemia group	X ²	P
sex	female	11	12	8.4068	0.0037**
	male	11	53		
hypertension	N	8	23	0.0069	0.9339
	Y	14	42		
diabetes	N	13	46	1.0271	0.3108
	Y	9	19		
hyperlipidemia	N	15	47	0.1366	0.7117
	Y	7	18		
smoking	N	14	40	0.0913	0.7625
	Y	8	25		
drinking	N	17	50	0.2307	0.631
	Y	5	15		
collateral circulation building	N	15	21	8.7206	0.0031**
	Y	7	44		

** P<0.01

Table 2 Logistic regression analysis

independent variable	β	P	OR (95% CI)
sex	-1.4213	0.0099	0.241 (0.080-0.728)
collateral circulation	1.4458	0.0067	4.245 (1.44 – 12.5)

Figures

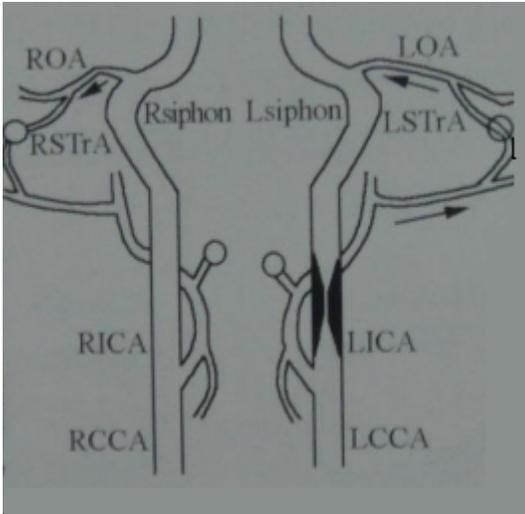


Figure 1

The change of the ocular artery and the supratrochlear artery. The right side is the normal condition and the left side is ocular collateral circulation building with regurgitant blood flow of ocular artery and the supratrochlear artery.

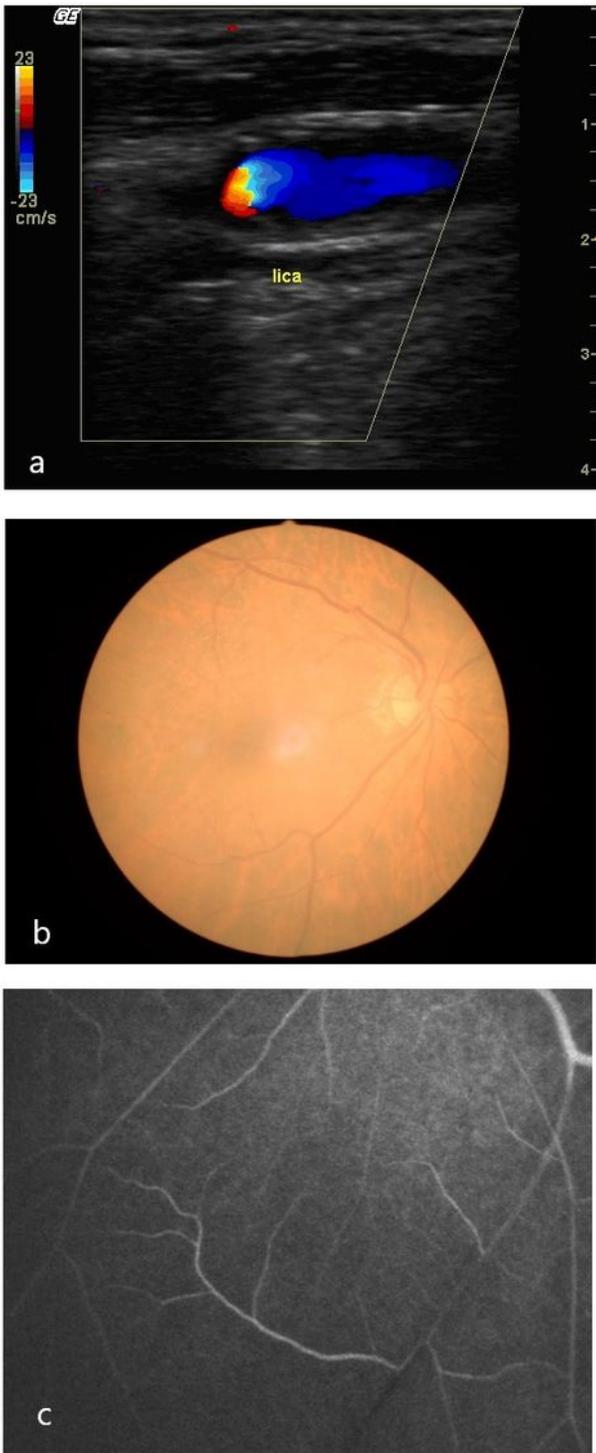


Figure 2

2a Example of CAO. Occlusion at the beginning of left internal carotid (carotid duplex ultrasonography).
2b Example of OIS in the same patient. Severe ischemia retina with thin arteries and dilated veins. 2c
Example of OIS diagnosis. Peripheral retinal ischemia (fluorescein angiography).

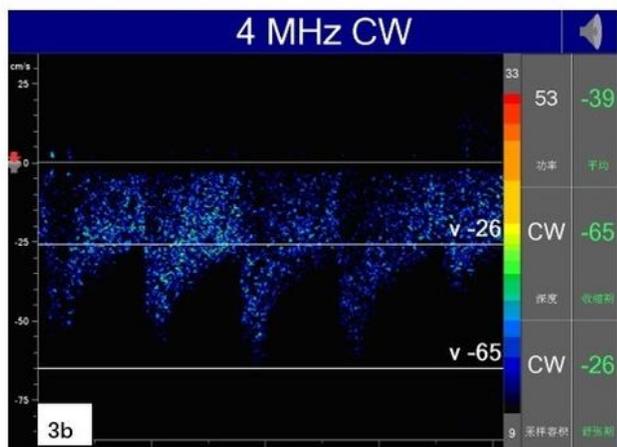
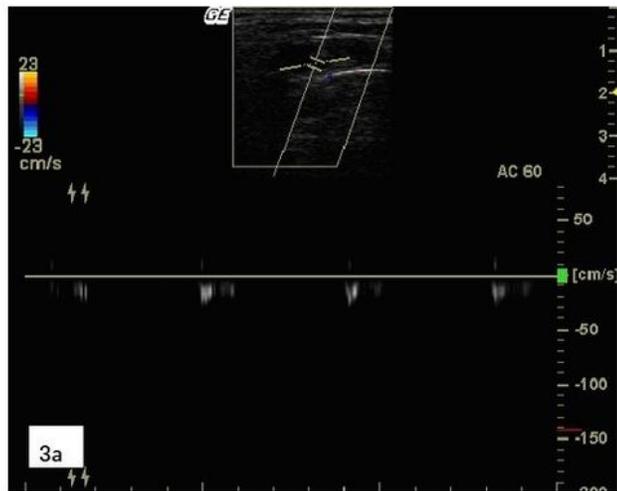


Figure 3

3a example of another CAO occlusion at the beginning of left internal carotid without blood flow signal detected (color Doppler flow imaging). 3b Example of collateral circulation building. Regurgitant blood signal detected in arteriae supratrochlearis via TCD, indicating collateral circulation building of artery ocular. 3c Example of the same patient's retina Lighter optic disc and peripheral cotton spots.