• Clinical Research •

Correlation of ischemic ophthalmopathy with lacunar infarction

Min Wang[1], Yu-Fang Gao[2,3], Wei Chen[3], Rong Li[4], Li-Hua Hou[1], Jian-Ying Du[1]

[1]Department of Ophthalmology, the First People's Hospital of Xianyang, Xianyang 712000, Shaanxi Province, China
[2]Department of Laboratory Diagnosis, the Central Hospital of Xianyang, Xianyang 712000, Shaanxi Province, China
[3]Xi'an Jiaotong University, Xi'an 710000, Shaanxi Province, China
[4]Department of Ophthalmology, the First Affiliated Hospital, Xi'an Medical University, Xi'an 710000, Shaanxi Province, China
Co-first authors: Min Wang and Yu-Fang Gao
Correspondence to: Wei Chen. Xi'an Jiaotong University, Xi'an 710000, Shaanxi Province, China. chenwei808@mail.xjtu.edu.cn
Received: 2019-03-21 Accepted: 2019-10-21

Abstract

● **AIM:** To investigate the correlation of ischemic ophthalmopathy (IO) with lacunar infarction (LI), an ischemic lesions in the cerebrovascular system.

● **METHODS:** Totally 204 cases of IO without any nervous system symptom and previously diagnosed LI served as the observational group. All 204 cases without IO, nervous system symptoms and previous LI served as the control group. Age and sex between the two groups matched well. LI was diagnosed by magnetic resonance imaging (MRI) and the results of the two groups were statistically analyzed and compared.

● **RESULTS:** IO included 174 eyes of 156 patients with non-arteritis anterior ischemic optic neuropathy (NAION), 42 eyes of 36 patients with central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) and 12 eyes of 12 patients with ocular ischemia syndrome (OIS). The detection rate of LI (72.54%) in IO group was obviously higher than that (15.68%) in the control group (P<0.001). IO was positively correlated with LI (r=0.573, P<0.05). In addition, most infarction sites located in the basal ganglia (67.57%), which were not the vital areas of cerebrum and not easy to be found due to their small size. The majority of those first visited IO patients (72.54%) without nervous system symptom and previously diagnosed LI had already suffered from LI.

● **CONCLUSION:** According to our studies, there is a positive correlation between IO and LI. IO can be used as an important predictor for the present of LI, especially obvious signs of the patient.

● **KEYWORDS:** ischemic ophthalmopathy; lacunar infarction; non-arteritis anterior ischemic optic neuropathy; central retinal artery occlusion; branch retinal artery occlusion; ocular ischemia syndrome

DOI:10.18240/ijo.2020.06.16

Citation: Wang M, Gao YF, Chen W, Li R, Hou LH, Du JY. Correlation of ischemic ophthalmopathy with lacunar infarction. *Int J Ophthalmol* 2020;13(6):960-964

INTRODUCTION

Ischemic ophthalmopathy (IO) is a group of diseases with pathological and physiological changes caused by ischemia of different tissues of the eye, which is one of the commonly encountered diseases in the Department of Ophthalmology[1-5], including non-arteritis anterior ischemic optic neuropathy (NAION), central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), ischemic optic neuropathy (ION) and ocular ischemia syndrome (OIS). Interestingly, most patients with IO were reported to have ischemic lesions in their cerebrovascular system (CVS)[2-6]. However, as visual functional impairment is the primary symptom of IO patients and there is light or no systemic symptoms, nervous system examination was easily neglected by ophthalmologists. Ischemic stroke is the general term of cerebral tissue necrosis caused by stenosis or occlusion of the cerebral artery (carotid artery and vertebral artery) and cerebral blood supply insufficient, which has the similar pathogenesis with IO[7-9].

IO is mainly due to carotid artery stenosis, as well as attachment and defluxion of atherosclerosis plaque caused by artherosclerosis[6-20]. Its occurrence is closely associated with age, sex, hypertension, diabetes, coronary heart disease and smoking, which also caused atherosclerosis[6-21]. Internal carotid artery system originates from the common carotid artery, which mainly supplies ocular region and three-fifths of anterior part of cerebral hemisphere. Its main branches include ophthalmic artery and arteria chorioidea, which

Table 1 The general disease history of IO subgroups and control groups *n* (%)

General disease	NAION (*n*=156)	Control group (*n*=156)	RAO (*n*=36)	Control group (*n*=36)	OIS (*n*=12)	Control group (*n*=12)
Hypertension	35 (22.4)	38 (24.4)	8 (22.2)	10 (27.8)	1 (8.3)	1 (8.3)
Diabetes	33 (21.2)	36 (23.0)	5 (13.9)	7 (19.4)	2 (16.7)	2 (16.7)
Hypertension and diabetes	6 (3.8)	5 (3.2)	3 (8.3)	3 (8.3)	3 (25.0)	4 (33.3)
No hypertension or diabetes	82 (52.6)	77 (49.4)	20 (55.6)	16 (44.5)	6 (50.0)	5 (41.7)
χ^2	0.216, 0.227, 0.224, 0.319		0.209, 0.207, 0.212, 0.331		0.119, 0.107, 0.120, 0.201	
P	0.729, 0.837, 0.801, 0.513		0.839, 0.917, 0.801, 0.521		0.989, 0.998, 0.981, 0.807	

NAION: Non-arteritis anterior ischemic optic neuropathy; RAO: Retinal artery occlusion; OIS: Ocular ischemia syndrome.

supplies corpora striata, hippocamp, lateral geniculate body, cerebral peduncle, mammillary body and gray tubercle. While artherosclerosis occurs in arteria carotis, especially the degree of narrowing exceeds 75%, ischemic lesions may occur in its supply areas. If complicated with microemboli and other predisposing factors, angiemphraxis diseases can occur at any time[22]. On this occasion, ocular diseases mainly including CRAO, BRAO, and OIS turns out. As far as the brain is concerned, three types of lacunar infarction (LI) are the most common diseases, including ischemic attack, cerebral thrombosis and cerebral embolism.

In order to clarify the correlation between IO and ischemic lesions in CVS and investigate whether IO can predict LI, this present study was conducted.

SUBJECTS AND METHODS

Ethical Approval The study protocol was approved by the Institutional Ethics Committee at First People's Hospital of Xianyang, and followed the principles of the Declaration of Helsinki. The informed consent was obtained from all patients.

Totally 204 inpatients with IO, who had no nervous system symptom and history of LI, were recruited to participate in this study in Department of Ophthalmology, the First People's Hospital of Xianyang, Xianyang, Shaanxi, China from October 2014 to October 2016. The IO group (132 male and 72 female) aged from 44 to 78y (mean age 60.7±3.4y). An age-and-sex matched control group consisted of 204 inpatients without IO from the Department of Ophthalmology, the First People's Hospital of Xianyang, Xianyang, Shaanxi Province, China, same endemic area and they also had no nervous system symptom and history of LI. Neurologists performed the diagnosis for LI.

Ischemic stroke diagnostic criteria in this article (including any one of the first items and 2-4): 1) there was no obvious symptoms and signs in the whole body; 2) nuclear magnetic resonance examination showed that brain edema, cerebral ischemia lesions in the low density region, and no hemorrhagic changes; 3) cerebral angiography found one or more of the main artery stenosis or occlusion of the change; 4) brain scan prompt and cerebral infarction except for brain tumors.

IO group included 144 eyes of 132 male patients and 84 eyes of 72 female patients. Age ranged from 44 to 78y (mean age 60.7±3.4y). In detail, IO group included 174 eyes of 156 patients with NAION, 42 eyes of 36 patients with CRAO or BRAO and 12 eyes of 12 patients with OIS.

All participants were then divided into NAION group (156 cases), RAO group (36 cases) and OIS group (12 cases). Based on their general condition: hypertension, diabetes, hypertension and diabetes and no hypertension or diabetes, no significant differences between IO subgroups and control groups were found (P>0.05; Table 1).

General medical examination was performed in all participants. Visual acuity, slit lamp microscope, fundus examination, ophthalmotonus, fluorescence fundus angiography (FFA), visual field, optical coherence tomography (OCT), visual evoked potential (VEP) and electroretinogram (ERG) were performed in the Department of Ophthalmology. Otherwise, auxiliary examinations were performed, including blood, urine and excrement tests, X-ray examinations, electrocardiography and neck ultrasound doppler. Head magnetic resonance imaging (MRI) was performed after getting the agreement from all clients to affirm if LI had existed. According to the inspection, three neurologists performed the diagnosis by the way of double-blind method. Finally, LI were definitely diagnosed by history, clinical manifestation, auxiliary examination results, and reference in combination[4]. Records of 204 IO patients and 204 control patients examined during a 24-month period were reviewed.

Experimental data were analyzed statistically by using the SPSS 13.0 software. The two groups of patients with body mass index, diabetes mellitus, hypertension, hyperlipidemia, high homocysteine, C reactive protein, smoking has confirmed incidence risk factors have influence on the two kinds of diseases on the logistic regression analysis, P<0.05 has statistical difference. The incidence of ischemic stroke in the two groups was adopted. χ^2 test was performed for differences among groups. A P value less than 0.05 was considered as statistically significant.

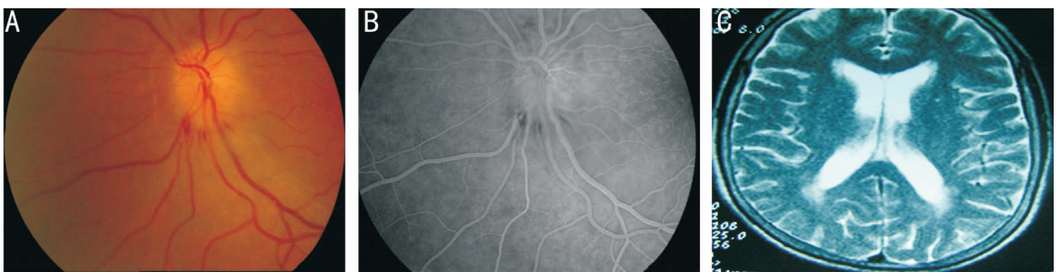

Figure 1 Images of a patient with anterior ischemic optic neuropathy in his left eye A: Fundus photograph showed the cord-like bleeding and edema underneath optic disc, which boundary was fuzzy; B: FFA image showed that fluorescence was shielded by the bleeding underneath optic disc, fluorescence leakage, and fuzzy papillary boundary; C: MRI showed multiple lacunar infarction (T2 high signal lesions) existed in the side of bilateral ventricle body and the basal ganglia.

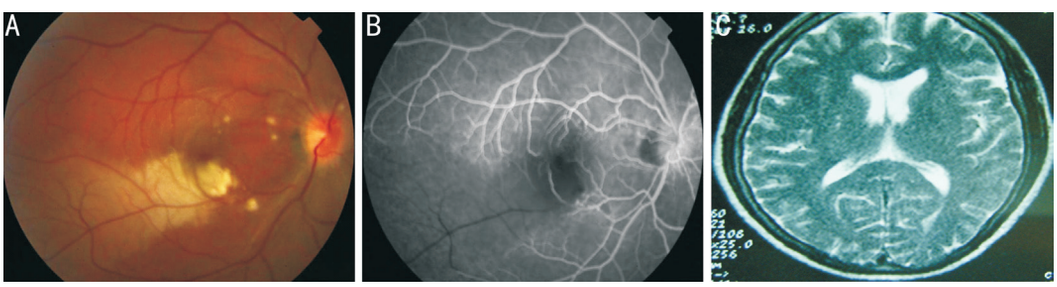

Figure 2 Images of a patient with branch retinal artery occlusion in his right eye A: Fundus photograph showed greyish edema in the inferotemporal retina due to branch arterial occlusion; B: FFA image showed filling defect in the field of inferotemporal branch arterial occlusion; C: MRI showed multiple lacunar infarction (T2 high signal lesions) existed in the right basal ganglia .

RESULTS

There was no statistical difference between the two groups of patients by logistic multi factor regression analysis (P=0.09), exclude the influence of systemic risk factors on the results. Among the finally diagnosed patients with LI, 148 case (72.54%) were in IO group and 32 cases (15.68%) were in control group. The difference of LI detection rate between the two groups was statistically significant (χ^2=21.501, P=0.000; Table 2). MRI detection rates of LI between the two groups had statistical difference (χ^2=21.501, P<0.001). The comparison of sex in LI patients of IO group was not statistically different (χ^2=0.241, P=0.612).

Among 148 cases of patients with LI in IO group, 84 cases were male patients (63.64% in all male patients) and 64 cases were female patients (88.89% in all female patients). The difference of LI detection rate between male and female gender was not statistically significant (χ^2=0.241, P=0.612). IO was positively correlated with LI (r=0.573, P=0.000).

Among the finally diagnosed patients with LI and positive MRI, 112 case (71.79%) were in NAION group and 24 cases (15.38%) were in control group. The difference of LI detection rate between the two groups was statistically significant (χ^2=20.401, P=0.000); the difference of intra-ocular tension between two groups was not statistically significant (t=0.901, P=0.954; Table 3, Figure 1). NAION was positively correlated with LI (r=0.569, P=0.000).

Table 2 Clinical manifestations of LI in IO group and control group *n* (%)

Groups	Positive MRI	Negative MRI	Total
IO group	148 (72.54)	56 (27.45)	204
Control group	32 (15.68)	172 (84.31)	204
Total	180	228	408

IO: Ischemic ophthalmopathy; MRI: Magnetic resonance imaging.

Table 3 Clinical manifestations of LI in NAION group and control group

Groups	Positive MRI (%)	Negative MRI (%)	Intra-ocular tension (mm Hg)
NAION group	112 (71.79)	44 (28.21)	15±2.15
Control group	24 (15.38)	132 (84.62)	14±2.23

NAION: Non-arteritis anterior ischemic optic neuropathy; MRI: Magnetic resonance imaging.

Among the finally diagnosed patients with LI and positive MRI, 26 case (72.22%) were in RAO group and 6 cases (16.67%) were in control group. The difference of LI detection rate between the two groups was statistically significant (χ^2=20.611, P=0.000); the difference of intra-ocular tension between two groups was not statistically significant (t=0.912, P=0.941; Table 4, Figure 2). RAO was positively correlated with LI (r=0.559, P=0.000).

Among the finally diagnosed patients with LI and positive MRI, 10 case (83.33%) were in OIS group and 2 cases

Table 4 Clinical manifestations of LI in RAO group and control group

Groups	Positive MRI (%)	Negative MRI (%)	Intra-ocular tension (mm Hg)
RAO group	26 (72.22)	10 (27.78)	16±2.06
Control group	6 (16.67)	30 (83.33)	15±2.13

RAO: Retinal artery occlusion; MRI: Magnetic resonance imaging.

Table 5 Clinical manifestations of LI in IOS group and control group

Groups	Positive MRI (%)	Negative MRI (%)	Intra-ocular tension (mm Hg)
IOS group	10 (83.33)	2 (16.67)	16±2.21
Control group	2 (16.67)	10 (83.33)	15±2.25

OIS: Ocular ischemia syndrome; MRI: Magnetic resonance imaging.

(16.67%) were in control group. The difference of LI detection rate between the two groups was statistically significant (χ^2=25.621, P=0.000); the difference of intra-ocular tension between two groups was not statistically significant (t=0.952, P=0.911; Table 5). IOS was positively correlated with LI (r=0.667, P=0.000<0.05).

DISCUSSION

Although the primary cause of all three diseases is different, some common pathophysiology of NAION, RAO, and OIS were the same. For example, atherosclerosis leads to carotid stenosis, atherosclerotic plaque attachment, shedding, and pressure difference between intraocular pressure and blood pressure due to the damaged balance between them[7-8]. In this study, general medical examination, detailed ophthalmology examination, laboratory examination and auxiliary examination were performed in all clients to confirm final diagnosis of LI. LI was diagnosed by MRI and verified by double blind method in order to rule out information bias in the process of the diagnosis. Thus, the results were reliable. Differences of age, sex and general disease history between IO group and control group were not statistically significant. However, MRI detection rates of LI in IO group were higher than that in control group. The comparison of sex in LI patients of IO group was not statistically different. IO patients often see a doctor due to their visual function impairment. If no or general malaise symptom is mild, the patient himself and ophthalmologists may neglect systemic and brain check. It has been reported in the domestic literature that IO can predict carotid artery stenosis[23]. In patients without cardiac embolic sources, cerebral microembolism is frequently present on the side of retinal ischemia, particularly during the week after onset of symptoms. It is often associated with severe stenosis or occlusion of the ipsilateral carotid artery[24]. Similarly, the results of this study showed that IO was obviously correlated with LI, which has not been not reported yet.

Based on this, after IO is finally diagnosed, systemic and brain examination, especially MRI, is necessary to affirm if LI occurs. Meanwhile, getting a physician consultation and making a final diagnosis is critical, in order to treat systemic diseases in time while treating the disease of eyes. In addition, this study also showed that 65.57% of infarction areas was basal ganglia but not the key regions of the brain. The lesion area was small and not easy to be found, so early etiological examination should be performed for this kind of patients. Meanwhile, according to the examination results, prophylactic treatment should be performed to reduce the risk of cerebrovascular accidents. There are some limitations in this study, which cannot completely indicate that ischemic stroke and IO have exactly the same risk factors. In the future, we will pay attention to this aspect.

According to our studies, LI incidence in IO patients was significantly higher than in non-IO ones, and there was a positive correlation between IO and LI. IO can be used as a predictor of LI, especially obvious signs of the patient. We expect the ophthalmologists to timely diagnose patients with ischemic lesions in CVS and give them positive and reasonable treatment in clinical practice.

ACKNOWLEDGEMENTS

Foundations: Supported by National Natural Science Foundation of China (No.81500726); Health Research Program of Shaanxi, China (No.2014E12); Shaanxi Health Research Foundation (No.2016E007).

Conflicts of Interest: Wang M, None; **Gao YF,** None; **Chen W,** None; **Li R,** None; **Hou LH,** None; **Du JY,** None.

REFERENCES

1 Song C. *Que-Xue Xing Yan Bing Zhi Liao Xin Gai Nian*. 2nd ed. Bei Jing: People's Military Medical Publishers. 2005;28-29.

2 Monigari N, Deshpande A, Nalabothu M, Rao S. Graves' disease presenting as unilateral anterior ischaemic optic neuropathy. *BMJ Case Rep* 2014;2014:bcr2013203222.

3 Wang M, Wang RS, Wang S, Chen XJ, Ma WT. Effect of ophthalmotonus intervention on ocular hemodynamics in patients with ischemic ophthalmopathy. *Chinese Journal of Ocular Fundus Diseases* 2013;29(6):553-556.

4 Wang M, Wang S, Xu SY, Chen XJ, Ma WT. Evaluation of retrobulbar hemodynamic changes in ischemic ophthalmopathy. *Journal of Clinical Ophthalmology* 2014; 22(1):19-21.

5 Wang M, Wang S, Xu SY, Chen XJ, Ma WT. Clinical study on retrobulbar hemodynamics change in ischemic ophthalmopathy. *Chinese Journal of Practical Ophthalmology* 2014;32(6):712-714.

6 Bernard, Zinman, Vora J, Nirmeyer M, Gall MA, Mathieu C. Acute and chronic complications. *Diabete*s 2013;62:99-172.

7 Terelak-Borys B, Skonieczna K, Grabska-Liberek I. Ocular ischemic syndrome-a systematic review. *Med Sci Monit* 2012;18(8): RA138-RA144.

8 Howard DPJ, van Lammeren GW, Redgrave JN, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM. Histological features of carotid plaque in patients with ocular ischemia versus cerebral events. *Stroke* 2013;44(3):734-739.

9 Ritzel RM, Pan SJ, Verma R, Wizeman J, Crapser J, Patel AR, Lieberman R, Mohan R, McCullough LD. Early retinal inflammatory biomarkers in the middle cerebral artery occlusion model of ischemic stroke. *Mol Vis* 2016;22:575-588.

10 Lawrence PF, Oderich GS. Ophthalmologic findings as predictors of carotid artery disease. *Vasc Endovascular Surg* 2002;36(6):415-424.

11 Ghaleh Bandi MF, Naserbakht M, Tabasi A, Marghaiezadeh A, Riazee Esfahani M, Golzarian Z. Obstructive sleep apnea syndrome and non-arteritic anterior ischemic optic neuropathy: a case control study. *Med J Islam Repub Iran* 2015;29:300.

12 Aggarwal D, Tan O, Huang D, Sadun AA. Patterns of ganglion cell complex and nerve fiber layer loss in nonarteritic ischemic optic neuropathy by Fourier-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53(8):4539-4545.

13 Nedelmann M, Graef M, Weinand F, Wassill KH, Kaps M, Lorenz B, Tanislav C. Retrobulbar spot sign predicts thrombolytic treatment effects and etiology in central retinal artery occlusion. *Stroke* 2015;46(8):2322-2324.

14 Chang YS, Chu CC, Weng SF, Chang C, Wang JJ, Jan RL. The risk of acute coronary syndrome after retinal artery occlusion: a population-based cohort study. *Br J Ophthalmol* 2015;99(2):227-231.

15 Duxbury O, Bhogal P, Cloud G, Madigan J. Successful treatment of central retinal artery thromboembolism with ocular massage and intravenous acetazolamide. *BMJ Case Rep* 2014;2014:bcr2014207943.

16 Chapin J, Carlson K, Christos PJ, DeSancho MT. Risk factors and treatment strategies in patients with retinal vascular occlusions. *Clin Appl Thromb Hemost* 2015;21(7):672-677.

17 Lin YC, Chen WC, Liao WC, Hsia TC. Central retinal artery occlusion and brain infarctions after nasal filler injection. *QJM* 2015;108(9):731-732.

18 Rodrigues IA. Acute and chronic spectral domain optical coherence tomography features of branch retinal artery occlusion. *BMJ Case Rep* 2013;2013:bcr2013009007.

19 Iijima H, Takahashi H. The final retinal thickness in eyes with branch retinal artery occlusion. *Br J Ophthalmol* 2012;96(10):1355.

20 Hultcrantz M, Pfeiffer RM, Björkholm M, Goldin LR, Turesson I, Schulman S, Landgren O, Kristinsson SY. Elevated risk of venous but not arterial thrombosis in Waldenström macroglobulinemia/lymphoplasmacytic lymphoma. *J Thromb Haemost* 2014;12(11):1816-1821.

21 Zheng W, Li YL, Sun YM, Bu YT, Yu XF, Yao W. Study on epidemiological characteristics and risk factors of stroke among adult residents in the urban areas of Tianjin. *Heart* 2011;97(Suppl 3):A93-A94.

22 Harsha KJ, Basti RS, Kesavadas C, Thomas B. Susceptibility-weighted imaging in carotido-cavernous fistulas. A case control study. *Interv Neuroradiol* 2013;19(4):438-444.

23 Zhao J, Hu LN, Wei SH. Clinical significance of ocular ischemia disease on predicted the happening of carotid stenosis. *Guoji Yanke Zazhi* 2009;9(2):361-362.

24 Wijman CA, Babikian VL, Matjucha IC, Koleini B, Hyde C, Winter MR, Pochay VE. Cerebral microembolism in patients with retinal ischemia. *Stroke* 1998;29(6):1139-1143.