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The application of optic disc capillary network density in the diagnosis and follow-up of primary glaucoma by optical coherence tomography angiography

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Abstract: *Backgroud Glaucoma is a group of irreversible blindness caused by retinal nerve fiber layer defect and visual field defect.Optical coherence tomography angiography(OCTA)can be used to observe optic disc vessels noninvasively.It is important for early diagnosis and follow-up of glaucoma to clarify the correlation between the density of optic disc capillary network and other observational indicators of glaucoma optic nerve damage.Objective By using optical coherence tomography angiography,clarify the correlations among optic disc capillary network density and retinal nerve fibre layer(RNFL)thinkness and mean deviation(MD)of visual field and mean cup disc ratio in primary glaucoma.To explore the role of this technique in the early diagnosis of glaucoma and monitor of the condition of the disease.Methods In this study,we collected 97 eyes of 61 subjects diagnosed with primary glaucoma.acute angle closure glaucoma group has 45 eyes of 31 case,chronic angle closure glaucoma group has 24 eyes of 14 case,primary open angle glaucoma group has 28 eyes of 16case.The image of optic disc capillary network,RNFL thickness and mean cup disc ratio were collected by OCTA.Image J was used to calculate the capillary network density in the cup disc image,and the mean deviation was obtained by using the full automatic perimeter to detect the visual field.Results Acute angle-closure glaucoma group:the optic disc capillary network density was 0.13±0.07%,RNFL thickness was 104.04±14.00μm,MD was 8.68±6.52dB,the mean cup disc ratio was 0.57±0.19;chronic angle-closure glaucoma group:the optic disc capillary network density was 0.12±0.06%,RNFL thickness was 104.08±17.12μm,MD was 7.05±6.37dB,the mean cup disc ratio was 0.57±0.20;primary open angle glaucoma group:the optic disc capillary network density was 0.15±0.05%,RNFL thickness was 111.71±9.16μm,MD was 5.30±4.37dB,the mean cup disc ratio was 0.53±0.16.Significant positive correlations were found between optic disc capillary network density and optic disc RNFL thickness(P<0.05),significant negative correlations were found between optic disc capillary network density and MD and mean cup disc ratio(P<0.05)by pearson correlations text in three group.Conclusions There is a clear correlation between optic disc capillary network density and optic disc RNFL thickness and MD and mean cup disc ratio in patients with primary glaucoma,the optic disc capillary network density can be used as reference for the diagnosis and follow-up of primary glaucoma.*

Keywords: *Glaucoma, Optical coherence tomography angiography, Optic disc capillary network density, Optic disc RNFL thickness, MD, Mean cup disc ratio*

1. Introduction

Glaucoma is a group of irreversible blindness caused by retinal nerve fiber layer defect and visual field defect.There are many theories about the pathogenesis of glaucoma. At present, optic neurovascular factors have been gradually confirmed to be one of the factors causing glaucoma optic nerve damage. Therefore, it is important to pay attention to the abnormal function of optic disc vessels for the diagnosis and treatment of glaucoma.In glaucoma patients,traditional auxiliary examinations

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have many limitations in monitoring the function of optic disc vessels.For example, classical fundus fluorescein angiography must be injected with contrast agents, which can lead to allergies, nausea and other adverse reactions.Color Doppler coherence tomography can only measure the large vessels of optic disc, but can not measure the vessels with small flow velocity[1-2].Laser Doppler Flowmeter and Laser Speckle Flowmeter have a small sampling range for the optic disc. The variation rate of the results measured for the diagnosis of glaucoma is high, so they can not be used as the best method to detect the optic disc blood flow[3].Now the new optical coherence tomography angiography technology provides us with the possibility to conveniently study the optic disc blood flow in glaucoma patients.OCTA is a non-invasive imaging technique for observing retinal and optic disc blood flow. In order to further determine the value of OCTA in the diagnosis and treatment of glaucoma, the correlation between the density of optic disc capillary network and other observational indicators of glaucoma optic nerve damage is clarified.In this study, OCTA was used to observe the density of optic disc capillary network in patients with primary glaucoma, to analyze the correlation between the density of optic disc capillary network and optic nerve damage in glaucoma, and to evaluate the value of OCTA in the early diagnosis and follow-up of glaucoma.

2. Materials and Methods

2.1 Inclusion and exclusion criteria for cases:

2.1.1 Inclusion criteria

(1) Primary acute angle closure glaucoma group(45 eyes of 31cases)Inclusion criteria

1) Patients aged 65-75

2) The contralateral eye had a clear history of acute angle-closure glaucoma attack, which had never occurred; there was no history of angle-closure glaucoma attack, but there was a clear family history of acute angle-closure glaucoma. Eye examination showed that there were certain anatomical characteristics of acute closure: shallow anterior chamber, narrow angle of chamber.

3) The patient had a history of acute glaucoma attack. After drug control, the intraocular pressure was less than 21 mmHg.Or without medication, the intraocular pressure drops to normal range.The patient had shallow anterior chamber, narrow angle, extensive adhesion of anterior chamber angle, fan-shaped atrophy of iris, dilated and fixed pupil and glaucoma spot of anterior lens capsule.There are or are no typical glaucomatous optic atrophy and visual field damage.

4) Except for those whose symptoms and signs are caused by other diseases of the whole body and eyes.

(2) Chronic angle closure glaucoma group(24 eyes of 14 cases)Inclusion criteria

1) Patients aged 65-75

2) The patient has a history of elevated intraocular pressure with no intraocular pressure-lowering drugs or drugs were used when seeing a doctor.Or there was no history of intraocular hypertension in this eye,but the contralateral eye was definitely diagnosed as chronic angle-closure glaucoma;

3) The slit lamp examination has the ocular anatomical characteristics of shallow anterior chamber and narrow angle.

4) Angular stenosis or adhesions could be seen under gonioscopy.

5) Characteristic damage (RNFL defect or optic disc morphological change) and/or glaucomatous visual field defect were found or not found in the fundus of the eye.

6) Except for those whose symptoms and signs are caused by other diseases of the whole body and eyes.

(3) Primary open angle glaucoma group(28 eyes of 16 cases)Inclusion criteri

1) Patients aged 65-75

2) Has a history of elevated intraocular pressure, did not use antihypertensive drugs or use antihypertensive drugs at the time of consultation;

3) The depth of anterior chamber was normal and the angle of anterior chamber was open.

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4) Characteristic damage (RNFL defect or optic disc morphological change) and/or glaucomatous visual field defect were found in the fundus of the eye.

5) Except for those whose symptoms and signs are caused by other diseases of the whole body and eyes.

2.1.2 Exclusion criteria:

1) Except for those who have a history of ophthalmic surgery and laser

2) Except for secondary glaucoma caused by inflammation, trauma or other causes,ocular diseases such as non-glaucomatous optic neuropathy, vascular or non-vascular retinopathy

3) Except for visual field defect caused by systemic diseases such as intracranial lesions

4) Except for refractive >-6.00D and >+6.00D, opacity between refractive eyes, unclear OCT images and poor coordination.

2.2 Method

2.2.1 Routine ophthalmological examination

All patients underwent relevant medical history collection, including age, sex, current medical history, etc. Routine eye related examinations included naked eye vision and best corrected vision, slit lamp microscopy, direct ophthalmoscope, UBM, etc.

2.2.2 Intraocular pressure (IOP)

IOP was measured by NIDEK (NT-510) non-contact tonometer. The patient's sitting position was measured three times continuously, and the average of the results was taken as a reference. The unit is mmHg.

2.2.3 View Field Humphrey 750i visual field analyzer

(Carl Zeiss, Germany) was used in this study.The center 30-2 standard full threshold program, white visual indicator No. III, 76 stimulus points and 31.5 ASB background light were used to monitor physiological blind spot fixation.The whole process is processed by computer and the results of visual field inspection are given.In order to ensure the accuracy of the results, this study only included the data of subjects whose fixation loss rate was less than 20%, false positive rate was less than 33%, and false negative rate was less than 33%.Patients were examined in darkroom.Corrective lenses were worn according to the refractive status of the subjects.Finally, the MD value of the eye was obtained by using the automatic analysis function of the perimeter.The MD value is the average of the difference between the monitoring value and the normal mean at all loci, indicating that the overall visual sensitivity of the subjects is higher or lower than the reference sensitivity of the normal people of the same age.The unit is dB.

2.2.4 Density of optic disc capillary network

Cirrus HD-OCT 5000 (Carl Zeiss, Germany) OCTA was used to examine the density of optic disc capillary network.The patient's optic disc was scanned to obtain a 3 mm x 3 mm image of the disc, and further to obtain the rheogram of the superficial retina, the deep retina and the choroidal layer of the patient.The blood supply of nerve fiber layer comes from superficial capillaries, so we choose superficial retinal vessels for measurement.The density of capillary network was defined as the proportion of capillary coverage area to the total area of optic disc (excluding the area of large vessels in calculation).The capillary network area A in the optic disc area can be obtained by processing and calculating the capillary network image obtained by using Image J software.The area B of the optic disc can be obtained by the function of optical nipple analysis (ONH).Finally, capillary network density C=A/B was obtained.

2.2.5 RNFL

The RNFL analysis function of Cirrus HD-OCT 5000 OCTA can be obtained directly.

2.2.6 Mean cup disc ratio

The ONH analysis function of Cirrus HD-OCT 5000 OCTA can be obtained directly.

The patients with high intraocular pressure in this study were treated actively by lowering intraocular pressure. After corneal edema disappeared, the required ophthalmological examinations

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were performed.

2.2.7 Statistical methods

Bivariate correlation analysis in SPSS 22.0 software was used to analyze the correlation between capillary density of optic disc and RNFL thickness, degree of visual field defect and average cup-disc ratio of optic disc.In this study, $P < 0.05$ shows that the difference is statistically significant.

3. Results

The Q-Q maps of capillary reticulum density, RNFL thickness, MD and mean cup disc ratio of the optic disc in three groups were plotted by SPSS software.Each sample point in the three groups is basically a straight line around the diagonal distribution of the first quadrant. It is considered that the sample conforms to the normal distribution.Pearson can be used to analyze the correlation between two variables.The following are the results of correlation analysis of the density of optic disc capillary network with the thickness of optic disc nerve fiber layer, visual field defect and mean cup disc ratio in three groups.

3.1 Primary acute angle closure glaucoma group(45 eyes of 31cases)

The optic disc capillary network density was 0.13±0.07%, RNFL thickness was 104.04±14.00μm, MD was 8.68±6.52dB, the mean cup disc ratio was 0.57±0.19;Significant positive correlations were found between optic disc capillary network density and optic disc RNFL thickness($P < 0.05$),significant negative correlations were found between optic disc capillary network density and MD and mean cup disc ratio($P < 0.05$,Table1)

3.2 Primary chronic angle closure glaucoma group(24 eyes of 14 cases)

The optic disc capillary network density was 0.12±0.06%, RNFL thickness was 104.08±17.12μm, MD was 7.05±6.37dB, the mean cup disc ratio was 0.57±0.20;Significant positive correlations were found between optic disc capillary network density and optic disc RNFL thickness($P < 0.05$),significant negative correlations were found between optic disc capillary network density and MD and mean cup disc ratio($P < 0.05$,Table2)

3.3 Primary open angle glaucoma group(28 eyes of 16 cases)

Table 1: Correlations of 45 eyes of 31 cases among optic disc capillary network density and RNFL thinkness and mean deviation and mean cup disc ratio in primary acute angle closure glaucoma group.

Cases	Research target	Mean± standard deviation	Pearson correlation coefficient	P
45 eyes of 31cases	mean cup disc ratio	0.57±0.19	-0.698	0.000
	MD	8.68±6.52dB	-0.757	0.000
	RNFL	104.04±14.00μm	0.752	0.000
	capillary network density	0.13±0.07%		

Table 2: Correlations of 24 eyes of 14 cases among optic disc capillary network density and RNFL thinkness and mean deviation and mean cup disc ratio in primary chronic angle closure glaucoma group.

Cases	Research target	Mean± standard deviation	Pearson correlation coefficient	P
24 eyes of 14cases	mean cup disc ratio	0.57±0.20	-0.579	0.003
	MD	7.05±6.37dB	-0.609	0.002
	RNFL	104.08±17.12μm	0.667	0.000
	capillary network density	0.12±0.06%		

The optic disc capillary network density was 0.15±0.05%,RNFL thickness was 111.71±9.16μm, MD was 5.30±4.37dB, the mean cup disc ratio was 0.53±0.16.Significant positive correlations were found between optic disc capillary network density and optic disc RNFL thickness($P < 0.05$),significant negative correlations were found between optic disc capillary network density and MD and mean cup disc ratio($P < 0.05$,Table3)

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Table 3: Correlations of 28 eyes of 16 cases among optic disc capillary network density and RNFL thinkness and mean deviation and mean cup disc ratio in primary primary open angle glaucoma group.

Cases	Research target	Mean± standard deviation	Pearson correlation coefficient	P
28 eyes of 16cases	mean cup disc ratio	0.53±0.16	-0.473	0.011
	MD	5.30±4.37dB	-0.571	0.002
	RNFL	111.71±9.16μm	0.427	0.020
	capillary network density	0.15±0.05%		

4. Discussion

Glaucoma has become the world's first irreversible blindness, because there are often no obvious symptoms in the early stage of glaucoma, patients themselves have no obvious feeling, the disease is very hidden, even in developed countries and high-income groups, less than half of the patients with glaucoma are diagnosed and treated in time.And even with the current standard treatment for glaucoma patients, some patients'visual function continues to deteriorate.This requires us to establish the prevention of blindness of glaucoma on the basis of scientific understanding of its occurrence and development, early diagnosis and effective treatment.

Primary glaucoma is the main type of glaucoma, which can be divided into two types: angle closure and open angle. Among them, angle closure can be divided into acute and chronic clinical manifestations.In the current clinical work, the commonly used screening and monitoring indicators of glaucoma are visual acuity, intraocular pressure, visual field and RNFL thickness in OCT.However, these examinations have their limitations. The decline of vision is not proportional to the severity of glaucoma, especially in patients with open-angle glaucoma, some patients can still retain 1.0 central vision in the late stage of the disease.The limitation of intraocular pressure lies in the fluctuation of its measurement results. It is difficult to objectively reflect the intraocular pressure level of patients at a certain stage by single intraocular pressure measurement at the time of consultation. Moreover, the intraocular pressure of patients with normal intraocular pressure glaucoma is actually within the normal range of statistics (10-21 mmHg).However, the relative "normal" intraocular pressure of this kind of glaucoma can also cause RNFL defect and corresponding visual field damage, so the diagnosis and monitoring of normal intraocular pressure glaucoma need to be carried out by comprehensive other examinations.Although visual field is currently recognized as the golden standard for evaluating glaucoma functional impairment, it can not reflect early structural impairment, and its measurement is subjective, and the repeatability is poor in some patients.Recent studies on the paradisc retinal nerve fiber layer (pRNFL) and the ganglion cell complex (GCC) in the macular region have proved that these observational indices are more sensitive than visual field and can be helpful for early detection of glaucoma[4].As we all know, the pathogenesis of glaucoma is complex. We should not rely on a single measurement data to diagnose and evaluate glaucoma. At present, optic neurovascular factors are gradually found to be one of the important factors causing glaucoma optic nerve damage.Observing the abnormal manifestations of optic disc vessels may have some significance in the early diagnosis, progress detection and curative effect evaluation of glaucoma.Traditional auxiliary examinations such as FFA, color Doppler coherence tomography and laser Doppler flow meter have many limitations. They can not be used as the best method to detect the blood flow of the optic disc. Therefore, it is still of great significance to find new auxiliary examinations which are helpful to clinical diagnosis.OCTA is a new angiographic technique in recent years. It differs from traditional FFA and indocyanine green angiography in that it can provide more accurate blood flow information than traditional fundus angiography without intravenous injection of contrast agent.This technique has unique advantages in the application of glaucoma. It can observe the morphology of retinal choroidal vessels and the changes of blood flow in different layers.Through one scan, we can get the blood vessels of superficial retina, deep retina and choroidal layer respectively.Many scholars believe that the superficial retinal vessels are more vulnerable to damage and are more closely related to the changes of RNFL thickness of the optic disc.Therefore, this study selectively observed the changes of capillary network density in the superficial retina of the optic disc for the diagnosis and monitoring of glaucoma.The application of this technique enables us to study the structural damage of glaucoma more thoroughly, reaching the microscopic analysis of tissue anatomy in vivo.Compared with other examinations, OCTA in the diagnosis of glaucoma can advance to the stage of microvascular changes, and its repeatability is high [5]. The results are not affected by the subjective factors of patients, and it is safe and non-invasive.Jia [6] et al. have noticed in a study that the decrease of blood perfusion in the optic disc occurs before

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visual field damage occurs.Wang et al. [7] use OCTA to study the optic disc perfusion in glaucoma patients. It was confirmed that the degree of sparsity of optic disc capillary network in glaucoma patients was significantly related to the severity of glaucoma.We can conclude that OCTA technology can make the early diagnosis and monitoring of glaucoma more convenient.According to previous studies by many scholars, there is no obvious correlation between the course of disease, best corrected visual acuity and age and capillary density [8]. We will not elaborate and analyze it in detail here.

From the results of this study, we can know that there is a correlation between the density of capillary reticulum and RNFL thickness, visual field defect and mean cup disc ratio in primary acute angle-closure glaucoma, chronic angle-closure glaucoma and primary open-angle glaucoma (all $P < 0.05$).By comparing the capillary network density of optic disc with RNFL thickness, there is a significant linear positive correlation between them.The density of optic disc capillary network is negatively correlated with MD and average cup-disk ratio, which indicates that the density of optic disc capillary network decreases with the increase of visual field defect and average cup-disk ratio.Therefore, we speculate that there should be a corresponding relationship between the index reflecting the structural changes of optic nerve and the density of capillary reticulum in the optic disc in primary glaucoma.Observation and tracking of the density of the optic disc capillary network can predict and evaluate the early damage of the optic disc structure in primary glaucoma and monitor the progress of the disease.At present, the most commonly used indicators for the diagnosis and monitoring of glaucoma are visual acuity, intraocular pressure, cup-disk ratio, visual field defect, RNFL thickness. These indicators play an important reference value for the guidance of medication, whether surgery or not and the choice of surgical methods.Through the above results, we can conclude that OCTA observation of the optic disc capillary network has certain reference significance for judging the condition of glaucoma patients.

Combining the views of many scholars and the results of this study,we speculate that the correlative mechanism of these glaucoma related factors is as follows:Persistent high intraocular pressure leads to decreased blood perfusion of optic disc, microcirculation disturbance and optic nerve malnutrition, together with other possible factors (metabolic diseases, cardiovascular diseases, immune factors, hereditary factors), it causes damage to retinal nerve fibers, and ultimately leads to thinning and atrophy of retinal nerve fibers layer. The clinical manifestations are decreased vision, enlarged cup-disk ratio and visual field. Damage.

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