

Clinical Applications of Non-Invasive Multimodality Imaging in The Evaluation of Ocular Ischemic Syndrome: A Case Study

Abdulhamid Alghamdi

Faculty of Medicine, Department of Ophthalmology, Taif University

Email: drghamdieye@hotmail.com; Tel: +99 733 44 88 Fax: +99 733 4567

ABSTRACT

Background: A 74 years old lady presented with bilateral sudden deterioration of vision over a period of 3 weeks. She is a known diabetic and hypertensive for the past 25 years. The patient denied associated neurological symptoms. The patient underwent a comprehensive non-invasive neuroimaging and retinal imaging. **Case Presentation:** The case study is about right sided occipital lobe infarction and right sided internal carotid artery stenosis with complete right ophthalmic artery occlusion resulted in right Ocular ischemic syndrome (OIS). Ocular findings showed normal swinging light reflex. Right eye showed rubiosis iridis, neovascularization of the disc. Left eye showed moderate non-proliferative diabetic retinopathy. There was lack of cerebellar and/or cortical constitutional symptoms.

Magnetic resonance angiography (MRA) imaging showed compromised right side internal carotid system and complete occlusion of the right ophthalmic artery. Magnetic resonance imaging (MRI) showed as well isolated right sided occipital lobe infarction. The patient received neurological and ocular treatment.

Conclusion: Painless sudden bilateral visual disturbance in an elderly individual should draw the clinician attention to possible cortical etiology inspite the absence of neurological symptoms. Non-invasive imaging techniques had been shown to be effective in the evaluation of symptomatic Ocular ischemic syndrome (OIS), which should be considered if the gold standards imaging techniques are relatively or absolutely contraindicated.

Keywords: Magnetic resonance angiography, Non-invasive imaging, Occipital lobe infarction, Ocular ischemic syndrome, Swept-source optical coherence tomography.

INTRODUCTION

Ocular ischemic syndrome (OIS) is a relatively uncommon eye condition induced by chronic ocular hypoperfusion. It is a disease of elderly with male predilection. On 1988, the estimated incidence was 7.5 cases per million persons every year, but clinically a higher incidence is noticed attributed to the natural aging of the population and the increased incidence of atherosclerotic diseases which are the main etiology of OIS^(1,2). Recently, researchers reported a 4% and 5% prevalence of carotid artery stenosis in the United State of America and Saudi Arabia respectavelly. Systemic hypertension, diabetes, hyperlipidemia, coronary heart disease, chronic kidney disease and smoking history are significant risk factors for atherosclerosis. Increasingly, the atherosclerotic predisposing disaeases becoming more prevalent especially in the developing countries including Saudi Arabia^(3,4).

Ocular ischemic syndrome is characterized by chronic ischemia of the anterior and posterior segment of the eye which result in a diverse clinical presentations based on the duration and severity of the internal carotid artery (ICA) stenosis and the presence or absence of collaterals^(5,6). OIS is presented with non-specific symptoms and signs, which create a diagnostic dilemma and it is easily misdiagnosed with the more common retinal vascular diseases such as diabetic retinopathy (DR) and central retin vein occlusion (CRVO). Early detection of

OIS is of great paramount since this condition may pecede a life-threatening conditions like carotid artery stenosis (CAS), stroke or myocardial infarction. The reported mortality rate with OIS is 40% in the 5 years. Dealy and or failure in the diagnosis of OIS may increase the risk of irreversible visual loss and death⁽⁷⁾.

The gold standards retinal imaging used in the diagnosis of OIS is fundus fluorescein angiography (FFA), which has the most specific signs of OIS. The arm-to-choroid time > 15 seconds, arm-to-retinal circulation time > 18 seconds, and retinal arteriovenous time > 11 seconds are considered to be positive. Generally, FFA is considered a safe procedure but, it has a wide range of adverse reactions reported to be severe in up to 0.56%. Death was reported in a rate of 1:100,000 as well. The main limitation of FFA is the need for fluorescein dye as a contrast, which is associated with wide range of adverse reactions. History of allergy to the fluorescein dye is considered an absolute contraindication⁽⁸⁾.

Non-invasive ocular and neuroimaging tools have developed rapidly and may provide the clinician with a significant diagnostic signs which is more quick, non-invasive and eliminate the need for special precutions specially in elderly patients with comorbidity. Swept-source optical coherence tomography (SS-OCT) a recent advance in OCT technology has significantly increased scanning speed, depth and scanning area with 3-dimentional depiction



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of the retinal and choroidal layers. Nowadays, with increased incidence of systemic vascular diseases SS-OCT provides a readily accessible diagnostic tool that could be used in the screening, evaluation and monitoring of vision threatening vascular diseases including OIS^(9,10).

Magnetic resonance angiography (MRA) involves registration of the blood movement within the blood vessels and suppression of the static tissue around. It can give detailed information about the severity and extent of the atherosclerotic lesion within the carotid system. One of the widely used projection imaging method is time of flight (TOF) which involve more selective inversion magnetization giving 100% sensitivity and 96.70% specificity⁽¹¹⁾.

Therefore, we report a unique presentation of very rare concomitant OIS and isolated occipital lobe infarction. We demonstrated the importance of utilizing the clinical skills combined with non-invasive diagnostic imaging in the evaluation, diagnosis and monitoring of elderly patient with vision as well as life-threatening condition.

CASE PRESENTATION

A 75-year-old lady presented to the eye clinic complaining King Abdulaziz Specialist Hospital, Taif City of profound painless loss of vision in both eyes three weeks prior to her presentation. She denied the presence of associated ocular pain, alteration of consciousness and weakness in the extremities. Past medical history showed that she is diabetic for 25 years, hypertensive for 30 years and hyperlipidemic. She underwent successful cataract surgery 6 years prior to the event of loss of vision. She is on regular treatment for her systemic diseases.

General neurology examination revealed conscious oriented normal motor, sensory and cerebellar exam.

Ophthalmologic examination (a slit lamp examination, an intraocular pressure measurement using a non-contact tonometer, and a fundus examination) were performed for both eyes. Visual acuity were 20/400 right eye, 20/150 left eye with best correction. Intraocular pressure of 29 mmHg right eye and 15 mmHg left eye. Full extraocular movement, orthophoric and normal reactive pupil. No afferent pupillary defect with swinging light reflex test. Slit-lamp examination of the right eye showed quiet conjunctiva, clear cornea, moderate caliber neovascularization of the iris (NVI) mainly in mid-periphery of the iris, intraocular lens central within the capsular bag. Fundoscopy of the right eye showed modest pale disc, mid-periphery blot hemorrhages, neovascularization of the disc (NVD), attenuated retinal arteries, dilated non-tortuous retinal veins (Figure 1).

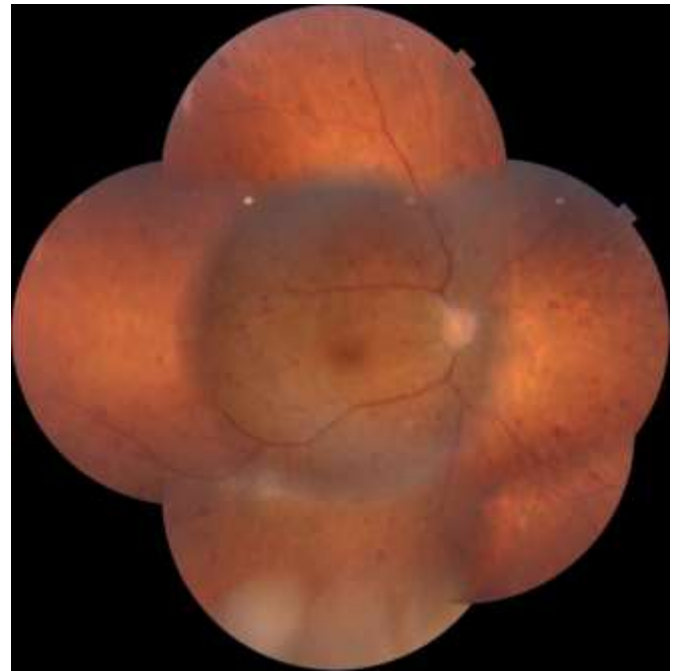


Figure 1: Fundus panoramic view. Right eye, mid peripheral petechial intraretinal hemorrhages and dilated non-tortuous veins. Absence of macular edema and hard exudates.

Slit-lamp examination of the left eye showed quiet conjunctiva, clear cornea, no neovascularization of the iris (NVI), intraocular lens central within the capsular bag. Fundoscopy of the left eye showed moderate non-proliferative diabetic retinopathy and dry macula (Figure 2).

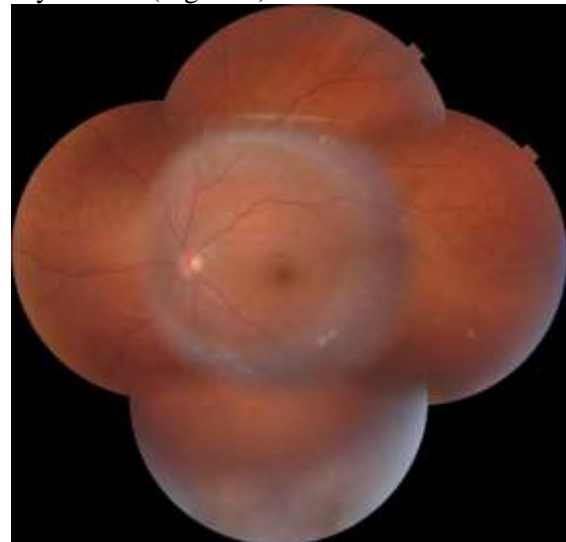


Figure 2: Fundus panoramic view. Left eye, healthy disc and dry macula. Retinopathy asymmetry demonstrated significantly.

Automated Humphrey visual field was not conclusive and patient could not perform the test. Confrontation visual field testing was performed by two masked examiners and both of them reported bitemporal hemianopia.

The refractive error was measured for each eye using an autorefractor which was as follow: -

Right eye : + 0.25 – 0.50 X 180

Left eye : + 0.50 – 0.25 X 175

Multi-modal imaging studies using swept-source optical coherence tomography

SS-OCT (Triton; Topcon Medical Systems, Tokyo, Japan) performed by two masked independent examiners and the results were recorded

and compared. Two good-quality 3-dimensional horizontal scans and horizontal line [3D(H) + Line(H)] across the fovea were obtained for each eye by each examiner using cube size 12.0 X 9.0 mm + 12.0 mm horizontal line across the optic disc and fovea. Generally, OCT showed outer retinal layers hyporeflective zone and thinning in the right eye, whereas normal foveal contour and retinal thickness in the left eye (Figure 3).

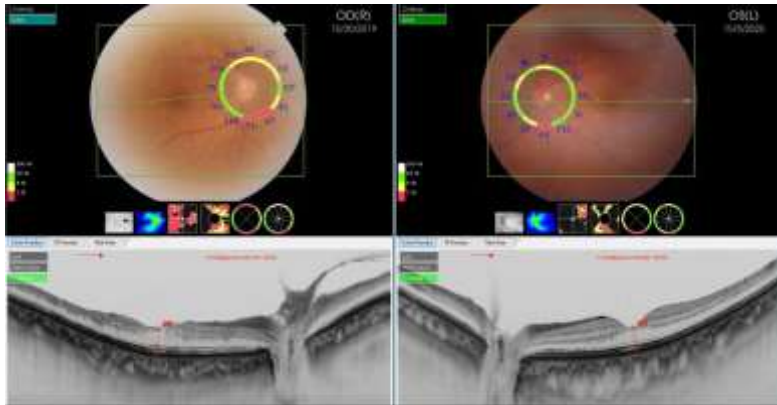


Figure 3: Swept-Source Optical Coherence Tomography SS-OCT (a) Right eye, the outer retinal layers (OPL and ONL) were dramatically reduced in thickness with hyporeflective signals indicating atrophic changes (b) Left eye, normal macular and retinal layers structures.

Choroidal thickness was defined as the distance from the outer border of the hyperreflective line, corresponding to the retinal pigment epithelium (RPE) perpendicular to the chorio-scleral interface⁽¹⁰⁾. Using the digital calipers provided by the Triton SS-OCT software, the subfoveal choroidal thickness (SFCT) was measured at the subfoveal region in each trans-sectional image of the horizontal macular scan and then averaged (Figure 4). The SFCT was measured by two independent observers (MF and AR) who were blinded to the data of each other. Retinal, choroidal and choroidal vessels luminal diameter measurements are summarized in (Table 1) .

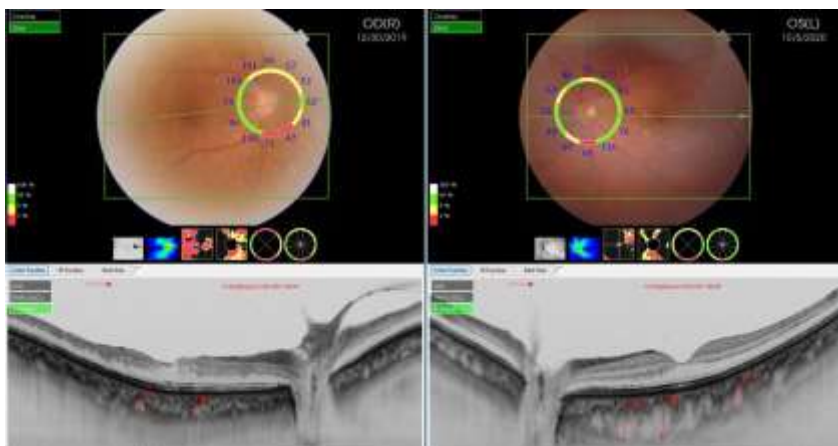


Figure 4: Swept-Source Optical Coherence Tomography SS-OCT (a) Right eye (OIS), the subfoveal choroidal thickness is significantly thinner as well as the mean luminal diameter were reduced. (b) Left eye, (control) the mean subfoveal choroidal thickness and the mean luminal diameter.

Table 1: Summary of average SS-OCT findings

Parameter	OIS eye (OD)		Normal eye (OS)	
	Examiner 1	Examiner 2	Examiner 1	Examiner 2
Foveal Retinal thickness(um)	205	209	251	225
Subfoveal Choroidal thickness(um)	246	256	453	382
Subfoveal Choroidal Vessele Luminal Diameter	78 , 81	93 , 98	271 , 212	211 , 251

The patient had previous history of allergy to fluoresceine dye. So the FFA test could not be done for her. MRI done for her showed recent right sided isolated occipital lobe infarction (Figure 5).

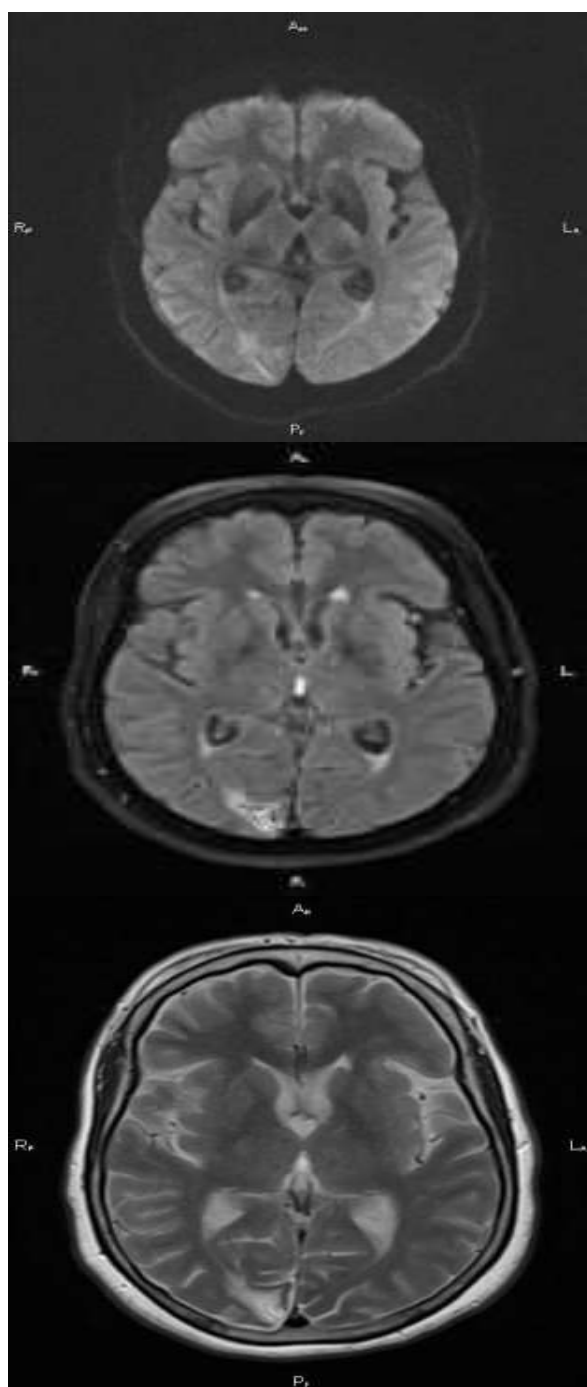


Figure 5: (a) MRI brain Axial T2WI, (b) Axial FLAIR and (c) diffusion-weighted images showed confined right occipital infarction.

Carotid Doppler ultrasound was done to evaluate the carotid system which showed moderate extracranial common carotid stenosis.

MRA was performed to study the intracranial carotid system which showed a significant narrowing of the right internal carotid artery and complete occlusion of the right ophthalmic artery (Figure 6).



Figure 6: TOF MRA shows the absence of flow-related enhancement of the right ophthalmic artery (a) Coronal MIP TOF MRA shows occluded right ophthalmic artery, (b) Axial TOF MRA. The left ophthalmic artery is patent. (c) Wall irregularities and luminal narrowing of the right ICA mostly secondary to atherosclerotic disease.

The patient was evaluated by neurologist and admitted for conservative management.

The patient received intravenous fluids, analgesics. The patient responded well to the IV thrombolytic therapy.

DISCUSSION AND CONCLUSION

Internal carotid artery disease (ICAD), defined as carotid plaques (CP) or carotid intima media thickness (CIMT), constitutes an independent predictor of ischemic stroke, cardiovascular ischemic disease and the overall mortality. Recent reports showed ICAD responsibility of 25% mortality rate during 10 year follow up. The ICAD is responsible about 20% – 40% of ischemic stroke. Stroke is the 2nd leading cause of death globally and the 3rd leading cause of disability in the United States of America. Early and accurate evaluation of the severity and characterization of ICAD plaque is of great importance to initiate the appropriate medical

and/or surgical intervention as well as initiation of the preventive measures^(10,11,12).

Majority of OIS patients have underlying comorbidities that are known atherosclerotic factors inducing carotid artery stenosis. Clinical features of OIS are widely variable, non specific and easily misdiagnosed with the more common neovascular ocular diseases, i.e. diabetic retinopathy (DR) and central retinal vein occlusion (CRVO). The most common presenting symptom is unilateral painless visual loss in almost all OIS patients. Only 20% reported periocular pain. The condition could be bilateral in 10% of cases. Majority, 65% of patients reported a constitutional neurological symptoms (headach, hemiplegia and syncope) and only 20%

reported coronary heart disease symptoms (palpitation, claudication) ⁽¹³⁾. Similar finding observed in our case where painless gradual loss of vision was the main presenting symptom. The constitutional symptoms were absent in our patient. Systemic hypertension and hyperlipidemia were the most commonly associated systemic diseases followed by diabetes as noticed in our case.

Among the reported cases with OIS most affected individuals presented with visual acuity less than 20/200. Longer disease course and the presence of constitutional neurological symptoms associated with poor visual prognosis. Primarily, OIS is a posterior segment disease with mid-peripheral scattered intraretinal dot and blot hemorrhages, cotton wall spots and microaneurysms being the most commonly observed posterior segment signs ⁽¹³⁾. Relatively dilated non-tortuous veins were observed in OIS as well. On the other hand, central retinal vein occlusion (CRVO), dilated tortuous retinal veins, diffuse dot and blot hemorrhages and severe oedema of the optic disc and the nerve fiber layer, which are pathognomonic signs. Absence of hard exudate and macular oedema helps to differentiate OIS from diabetic retinopathy. The most common anterior segment sign of OIS is neovascularization of the iris (NVI) which tend to be medium to large caliber mid-peripheral neovessels compared to the small caliber confluent pupil margin neovascularization associated with diabetic retinopathy. Majority of OIS patients initially present to neurology or cardiology departments with non-ocular constitutional symptoms. Isolated unilateral occipital cortex infarction is a very rare condition and diagnosis could be very difficult especially in the absence of associated cerebellar signs, i.e. gait imbalance and limb discoordination ^(13,14).

Our patient had unique presentation with bilateral painless loss of vision affecting the right eye more than the left with normal pupil reaction. Automated visual field could not be evaluated because of the very poor cooperation however, confrontation visual field testing showed bitemporal hemianopia. Loss of vision in our patient in the right eye could be explained by the ocular ischemic syndrome. While the loss of vision in the left eye with normal pupil reaction and normal fundus (asymmetric retinopathy) are key diagnostic findings of cortical infarction ⁽¹⁵⁾. In our patient left occipital cortex infarction was demonstrated with magnetic resonance imaging. The most common type of visual field defect in occipital cortex is congruous homonymous hemianopia (HH) ⁽¹⁶⁾.

We recommend all above 60 year individuals with moderate to severe ICAD to be referred routinely to ophthalmologist for ocular

evaluation. On the other hand, ophthalmologist should survey suspected OIS patients about neurological and cardiovascular symptoms, since early detection of life threatening neurological and or cardiovascular condition may initiate the appropriate timely management and eventually reduce mortality ⁽¹⁷⁾.

Spectral domain optical coherence tomography (SD-OCT) has been used to quantify and visualize changes in retinal and choroidal thickness in ipsilateral OIS eyes ⁽¹⁸⁾. The subfoveal choroidal thickness is significantly thinner in OIS eyes compared to the fellow unaffected eyes. Several reports demonstrated impaired choroidal circulation in eyes with OIS. The mean choroidal area and the mean luminal area were also reduced in OIS eyes compared to the control. The choroidal thickness and luminal area reduction may reflect the status of the ocular perfusion as a result of compromised carotid arterial system ^(19,20).

To the best of our knowledge this is the first report of swept-source optical coherence tomography (SS-OCT) used to study the choroidal changes in a patient with unilateral OIS. It was evident that the subfoveal choroidal thickness is reduced in the affected eye of our case compared to the contralateral eye. The reported retinal changes in OIS is segmental hyperreflective inner retinal layers evident between the outer plexiform layer (OPL) and the ganglion cell layer (GCL) more prominent in the peri-venous areas. This finding also seen in other retinal vascular conditions with reduced arterial blood flow i.e. branch and/or central retinal arterial occlusion. Also, the prominent middle limiting membrane sign (p-MLM) corresponding to hyperreflective band at the level of the outer plexiform layer (OPL) had been described in acute ischemia in CRVO as well as OIS. The OPL is the outermost layer of the retinal vascular supply and the most prone region to ischemic damage. The retinal layers structures and thickness were not significantly affected in OIS ⁽²¹⁾. Whereas, in our patient there was a significant hyperreflective inner limiting membrane and another hyperreflective band at the level of the OPL. The outer retinal layers (OPL) and Outer nuclear layer (ONL) were dramatically reduced in thickness with hyporeflexive signals indicating atrophic changes. Those observations may be explained by the chronicity of the OIS and the level of choroidal circulation deficiency.

Optical coherence tomography angiography (OCTA) has been involved in the evaluation of the functional blood flow without the need for intravenous dye in many ocular vascular diseases including ocular ischemic syndrome. OCTA showed a significant reduction of the superficial retinal

vascular perfusion⁽²²⁾. It showed comparable diagnostic capability in ischemic optic neuropathy to fluorescein based imaging⁽²²⁾. OCTA effectively delineates the anatomical relationship and origin of the neovascularization and helps monitor response to intravitreal and/or laser treatment. On the other hand, OCTA has significant limitations including sensitivity to motion since the imaging technique need repeated scanning of the same retinal structure using motion contrast. This fact makes imaging of poor visual acuity patients so difficult with a lot of motion artifact. Same difficulty was encountered in our case. Along with the inability to assess the vascular permeability and the interpretation variability between OCTA manufacturer display.

Magnetic resonance angiography (MRA) is a preferred neuroimaging study for the orbital as well as the cerebral vascular system. The three-dimensional time of flight (TOF) MRA specifically has high soft tissue resolution, non-invasive and radiation free technique that had been applied successfully in the evaluation of the ophthalmic artery anomalies^(23,24). MRA has very high sensitivity 98% and 100% specificity for complete occlusion of the carotid artery. To the best of our knowledge this is the first time TOF-MRA utilized in the evaluation of the level of occlusion of the ophthalmic artery in OIS patient. In our case we were able to demonstrate the yield of TOF-MRA in complete occlusion of the ophthalmic artery. MRA has certain limitations including metallic implant, obesity and claustrophobic individuals⁽²⁵⁾.

Early detection of choroidal circulation deficiency may prevent irreversible visual impairment in individuals with asymptomatic carotid artery disease. Ocular manifestations may precede or follow cerebrovascular complications of ICAD. Bilateral painless loss of vision with normal swinging pupillary light reflex should draw the attention of the ophthalmologist to possible cerebrovascular pathology. History of gait imbalance, uncoordinated movement of the limbs and vertigo should be included in the systemic review during history taking for such patients⁽²⁶⁾.

Late presentation is associated with poor visual prognosis. Previous reports showed that poor visual acuity at presentation (less than 20/200), the presence of iris neovascularization and neovascular glaucoma are considered as poor visual prognosis determinants. Most patients with OIS experienced deterioration of vision in the first year of diagnosis ending up with counting finger or worse vision⁽²⁷⁾.

carotid artery angioplasty and stenting (CAAS) is an emerging treatment option greatly improves the ocular blood flow to the normal levels within the ophthalmic artery (OA), posterior ciliary

artery (PCA) and central retinal artery (CRA). As reported CAAS if performed early in the OIS disease spectrum, i.e. before the iris neovascularization (NVI) onset showed significant shortening of the arm-retinal circulation time and normalizing the ocular perfusion within the OA, PCA and CRA. It significantly stabilize the best corrected visual acuity (BCVA) over a period of 12 months in OIS patients without NVI whereas, OIS patients showed variable visual acuity deterioration during the same follow up period⁽²⁸⁾.

This case has highlighted the importance of considering cerebrovascular stroke in the differential diagnosis of bilateral painless loss of vision among elderly patients. Careful evaluation, diagnosis, and the prompt initiation of the appropriate supportive care are highly recommended.

It is crucial to establish early diagnosis and initiate on time proper intervention. Effective screening tools need to be applied to determine the predictors of OIS development. Non-invasive imaging modalities should be applied and developed to establish an early diagnosis of ocular hypoperfusion. The presence or absence of collaterals, the ocular blood flow characteristic at the level of the OA, CPA, CRA and genetic predisposition may be utilized to determine the risk of certain individual to develop OIS.

Declarations

Ethical approval and consent to participate

Written ethical approval and informed consent from study participant **and faculty of Medicine, Taif University were obtained.**

Consent for publication

Written informed consent from study participant was obtained.

Availability of data and materials

The datasets used and analysed during the current study are available from the author on reasonable request.

Competing Interest

The author declares no competing interest.

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Author contributions

The author has solely contributed for this research.

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