ORIGINAL ARTICLE

NON ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY; DOES ANTICOAGULATION HELP?

Akhunzada Muhammad Aftab, Mustafa Iqbal, Awais Rauf, Asif Ali

Department of Ophthalmology, Khyber Teaching Hospital, Peshawar-Pakistan

Background: Non Arteritic Anterior Ischemic Optic Neuropathy (NAION) is the most common acute optic neuropathy in patients over 50 years of age. This study was conducted to determine the beneficial effects of anticoagulation with Heparin and Warfarin in patients with NAION presenting within 4 weeks of onset of symptoms **Methods:** A prospective, interventional, pilot study was conducted in Eye- A unit of Khyber Teaching Hospital from July 2010 onwards on patients with NAION presenting within 4 weeks of onset of symptoms. Patients underwent complete ophthalmological examination including Snellen's visual acuity (latter converted to Log MAR), pupil examination, fundus examination and automated Humphrey visual field analysis. Hematologic tests, Thrombophilia screening, Echocardiography and carotid Doppler ultrasound were carried on patients. All patients were anticoagulated with Heparin and Warfarin after obtaining informed written consent. Patients were examined at 1 Month, 3 months and 6 months' time period. Primary parameter measured was improvement in visual acuity. **Results:** Total number of patients in our study was 24. Regarding visual outcome total number of patients having significant improvement of visual acuity in our study was 16 (66.6%), while 4 (16.7%) patients had marginal improvement of visual acuity. Three (12.5%) patients maintained stable visual acuity of 6/6 throughout the study period in presence of thrombophilic disorders. One patient (4.1%) suffered a decline in visual acuity compared to VA at baseline presentation. **Conclusions:** Anticoagulation using heparin and warfarin does benefit patients with NAION presenting within 4 weeks of onset of symptoms. In our study a higher proportion of patients experienced significant improvement of visual acuity following anticoagulation as compared to the highest reported spontaneous improvement in such patients.

Keywords: Non Arteretic Anterior Ischemic Optic Neuropathy; Anticoagulation; Warfarin

J Ayub Med Coll Abbottabad 2016;28(4):776–80

INTRODUCTION

Non Arteritic Anterior Ischemic Optic Neuropathy (NAION) is the most common acute optic neuropathy in patients over 50 years of age[1], although it can present at an earlier[2] age. After glaucoma, it is the second most common cause of optic nerve related permanent visual loss in adults. Majority of cases are sporadic but familial cases have also been reported.[3] Patients usually present with sudden, painless, monocular deterioration of vision.[4] Some, however present with slight blurring and a normal or near normal visual acuity. Recurrences in the involved eye are rare; contralateral recurrence occurs in approximately 15% of patients.[5]

Approximately 1.2 Million axons of the Retinal Ganglion Cell layer (RGC) comprise the optic nerve. Theses axons are arranged into approximately 600 bundles, each carrying around 2000 axon fibres.[6] The peripapillary arteries (PPA), also known as the circle of Haller and Zinn supply the optic nerve head in the region of lamina cribrosa (LC). The PPAs are branches of the Short posterior ciliary arteries (SPCA) and form a complete or an incomplete ring of anastomoses around the optic nerve head in region of LC.[7] Ischemia of the optic nerve head in region of LC is termed Anterior Ischemic Optic Neuropathy (AION). with 2 major variants:

Arteretic Anterior Ischemic Optic Neuropathy, which is due to Giant Cell Arteritis

- Non Arteretic Anterior Ischemic Optic Neuropathy (NAION)

Despite the controversies regarding the distributary variations and characteristics of SPCA anastomoses around the optic nerve head, it has been proved, that, this circle provides segmental supply to the optic nerve head and physiologically acts as end arteries.[7]

Pathophysiology of NAION seems to be multifactorial. There are some well recognized risk factors while some studies have shown intrinsic disorders of regulation of coagulation as an additional risk factor.[8,9] Systemic vascular endothelial dysfunction and changes in Ocular Perfusion Pressure (OPP) have also been implicated as a risk factor[10–12].

Thrombotic and (or) embolic events leading to occlusion and (or) stenosis of these short posterior ciliary arteries leads to the segmental deterioration of function. Many believe cerebral stroke and Non Arteritic Anterior Ischemic Optic Neuropathy share

the same pathogenic mechanism. While others, consider it to be a hypotensive disorder.[13]

We postulate, hypotension and (or) thrombotic/embolic event leads to decreased perfusion pressure of the optic nerve head blood supply. This leads to sluggish blood flow through the SPCA's which in turn leads to arterial sludging predisposing to formation of a thrombus. The ischemic insult affected through this mechanism causes optic nerve head oedema and disruption of axonal flow leading to nerve fibre layer (NFL) swelling. This evokes a vicious cycle further compromising blood supply to optic nerve head.

On the other hand, congenital abnormalities of blood (Thrombophilia) directly predisposes to the formation of a thrombus and (or) occlusion of the SPCA's via embolism. This evokes the same vicious circle already mentioned.

Several studies have shown high prevalence of multiple risk factors. These may be considered as local or systemic factors

- Hypertension[14,15]
- Diabetes Mellitus[14,16]
- Hyperlipidaemia
- Ischemic heart disease
- Nocturnal hypotension[14,15]
- Sleep Apnoea[17,18]
- Absent or small cup in optic disc, and many others.[13]

Few prospective studies have evaluated the natural history of visual out come in Non Arteritic Anterior Ischemic Optic Neuropathy in patients seen within 2 weeks of visual loss.[13,19,20] They have reported a spontaneous improvement in visual acuity ranging from 26–43% at 6 months.

Non Arteritic Anterior Ischemic Optic Neuropathy represents an ischemic disorder of the short posterior ciliary artery circulation in the optic nerve head. As postulated earlier, hypotension and (or) thrombophilia leading to decreased perfusion pressure of the SPCA's cause sluggish blood flow leading to arterial sludging and predisposes to thrombus formation. The resultant Optic nerve head ischemia causes swelling and oedema, further compromising the perfusion due to pressure effects. The deleterious effects of ischemia could be relieved by anticoagulation as this possibly prevents thrombus formation in SPCA's with arterial sludging and helps to enhanced blood circulation through the already stenosed arteries.

Patients having intrinsic disorders of regulation of coagulation like Protein C, S and anti-thrombin III deficiency would benefit from long term anticoagulation, as has already been suggested by some authors of previous studies.[8]

As the international normalized ratio (INR) is raised, the chances of thrombus formation and thus ischemia of optic nerve head is reduced despite having a sluggish flow. As the perfusion to the optic nerve head improves, the oedema resolves, which leads to further beneficial effects of the therapy.

MATERIAL AND METHODS

A prospective, interventional pilot study was conducted from July 2010 onwards in Eye- A Unit of Khyber Teaching Hospital on patients with Non Arteritic Anterior Ischemic Optic Neuropathy (NAION). Diagnosis of NAION was made with the following criteria:

- Positive clinical history of sudden painless visual loss/ blurring of vision.
- Presence of risk factors.
- Reduced/ Near normal visual acuity.
- Presence of relative afferent pupillary defect (RAPD).
- Diffuse or Sectorial optic nerve head edema.
- Central and (or) Altitudinal field defect on Humphrey's visual field.
- Normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

Approval for the study was taken from the Ethical Committee of the hospital. Detailed history was taken from all the patients. All patients underwent the following clinical tests:

- Visual acuity using the Snellen's visual acuity charts. The readings were converted to Log MAR equivalents using a conversion table.
- Visual acuity was recorded taking care to avoid eccentric fixation.
- Pupils examination
- Dilated fundoscopy using 78D or 90D lens (Volk, USA).
- Automated visual fields examination using the Humphrey Visual Field Analyzer (Dublin USA).
- Haematological tests: Complete Blood Counts (CBC), Erythrocyte Sedimentation Rate (ESR), C- Reactive Protein (CRP), Prothrombin time (PT), Activated Partial Thromboplastin time (APTT), Fasting Lipid Profile (FLP).
- Echocardiography (Echo)
- Carotid Doppler
- Urine Routine Examination (Urine R/E)

Patients with normal PT and APTT were further analysed for Protein C and S deficiencies and those with prolonged PT and (or) APTT were analysed for Factor V Laiden Mutation, Fibrin Degradation Products and Anti thrombin III levels.

Patients with high (>140/90 mmHg) Blood Pressure readings were subjected to 8- Hourly BP monitoring. Diabetics were also investigated for

Glycosylated Haemoglobin Levels (HbA1c), Daily Fasting blood glucose, Post prandial blood glucose and 8- hourly Blood glucose monitoring. Diabetics and hypertensive patients were intensively managed with Insulin and (or) Oral hypoglycaemic and anti-hypertensive drugs. Statins were given to those with hyper lipidemia.

All the patients were given detailed information about the nature of this study. Written informed consent regarding anticoagulation (Heparin, Warfarin) therapy was taken from all the patients. Prior opinion from physician regarding any contra indication to anticoagulation therapy was obtained. Patients were started on Inj. Heparin 10,000 Units I.V Stat followed by 7,500 Units I.V T.I.D and Tab. Warfarin 10mg Stat followed by 5 mg P.O once daily. Inj. Heparin was stopped once International Normalized Ratio (INR) of 2.0 or above was achieved. Dose of Tab. Warfarin was adjusted to maintain INR in range of 2.0–3.0. INR was checked weekly in the first month and two weekly thereafter.

Patients were followed at 1 week, 1 month, 3 months and six months interval. The outcome measured was visual acuity (VA) using Snellen's visual acuity chart and number of lines of improvement.

Patients who achieved 3 or more lines of improvement using the Log MAR conversion chart were considered to have significant visual improvement. Those having improvement of less than 3 lines were considered to have marginal improvement.

RESULTS

Total number of patients in our study was 24. Total number of males was 15 (62.5%), while 9 (37.5%) were females. Mean age at presentation was 57 years (range 19–60 years). All (100%) had a positive clinical history of sudden painless loss/ blurring of vision in the affected eye and presented within 4 weeks of onset of symptoms (range 3 days to 4 weeks). Total number of diabetics alone was 2 (8.3%), Hypertensive only patients were 3 (12.5%) while 14 (58.3%) suffered both from diabetes and hypertension. 5 (20.8%) were neither diabetics nor hypertensive. Patients with hyper lipidemia were 10 (41.6%). Twenty-one (87.5%) patients had an RAPD on the affected eye, the rest had optic atrophy on the other eye. There was an altitudinal field defect in 11 (46%) of the eyes, while others had central and (or) nonspecific defects

Dilated fundus examination revealed swollen optic disc on the affected eye in all the patients while 3 (12.5%) had optic atrophy in the other eye as well, which was assumed to be due to a previous attack of NAION in the fellow eye. One patient had concomitant Oculomotor nerve palsy as well.

Investigations revealed normal ESR in all (100.0 %) and high CRP levels in 2 (8.3 %) patients. Carotid Doppler did not show significant (more than 60%) stenosis in any of the patients, however, plaques were seen in 9 (37.5%) patients. Echocardiography revealed abnormalities including diastolic dysfunction (DF) in 15 (62.5%), mitral regurgitation (MR) in 3 (12.5%), aortic regurgitation (AR) in 2 (8.3%), mitral valve prolapses (MVP) in 1 (4%), while 8 (34%) patients had a normal study.

One (4%) patient was found to be Protein C deficient, 1 (4%) was Protein S deficient and 1 (4%) patient had both Protein C and S deficiency in our study. One patient was suffering from Hepatitis C and was taking interferon treatment.

Regarding visual outcome (Figure-2) total number of patients having significant improvement of visual acuity in our study was 16 (66.7%), while 4 (16.7%) patients had marginal improvement of visual acuity. Three (12.5%) patients maintained stable visual acuity of 6/6 throughout the study period. One (4%) patient suffered a decline in visual acuity compared to VA at presentation. This patient also suffered a Mean Deviation (MD) loss of -10.28 dB.

Average lines of improvement were 5.6 Log MAR lines compared with base line visual acuity in significant improvement group (Figure-3). Mean duration of follow up was 7 months (range 1 month to 17 months). One patient had a decline of 5 lines in this study.

Four patients developed side effects of the therapy (raised INR above 4.0). In these, treatment had to be temporarily stopped. One of them required FFP's transfused. After re-achieving the target INR, they were discharged.

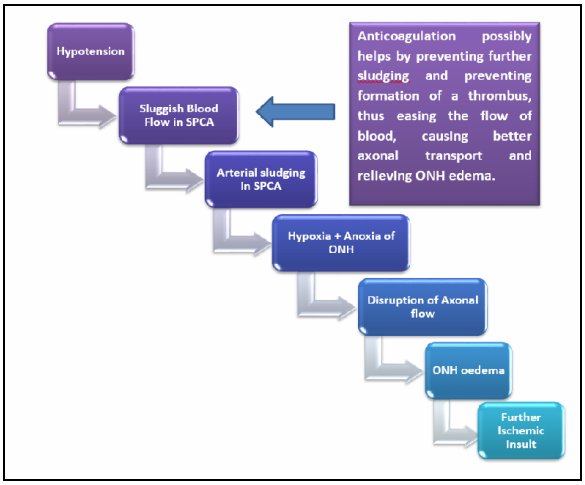

Figure-1: Schematic Algorithm of our proposed pathophysiology of NAION and rationale for Anticoagulation

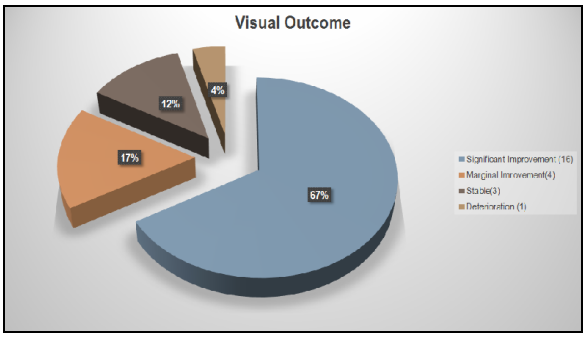

Figure-2: Visual acuity outcomes after last follow up visit

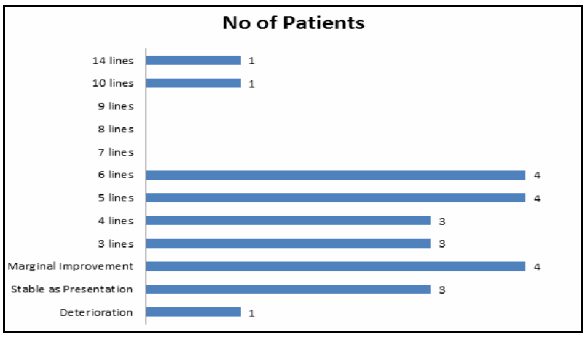

Figure-3: Number of patients having improvement in VA following anticoagulation

Table-1: Risk Factors and Change in visual acuity

DM	HTN	ESR & CRP	FLP	PT & APTT	ECHO	CAROTID DOPLER	PRO. C	PRO. S	Impro-vement Log MAR	V.A (Admission)		VA (Final)	
										Snellen	LogMAR	Snellen	LogMAR
Y	Y	N	N	N	DF	N	N	N	5	6/18	**0.5**	6/6	**0.0**
Y	Y	N	N	N	N	N	N	N	MI	PL +ve	**3.0**	3/60	**1.3**
Y	Y	N	N	N	AR,DF	N	N	N	MI	PL +ve	**3.0**	3/60	**1.3**
N	N	N	N	N	N	N	N	Def	0	6/6	**0.0**	6/6	**0.0**
N	N	N	TG	N	N	N	N	N	MI	PL +ve	**3.0**	3/60	**1.3**
Y	N	N	N	N	N	N	N	N	0	6/6	**0.0**	6/6	**0.0**
N	N	N	N	N	N	N	N	N	3	6/36	**0.8**	6/18	**0.5**
Y	Y	CRP	N	N	N	N	Def	Def	14	PL+	**3.0**	6/5	**-0.1**
Y	N	N	N	N	N	N	N	N	6	6/36	**0.8**	6/9	**0.2**
Y	Y	N	HDL	N	MR, IHD, E/A R.	N	N	N	3	6/18	**0.5**	6/9	**0.2**
Y	Y	N	CHOL	N	DF	N	N	N	4	6/24p	**0.6**	6/9	**0.2**
Y	Y	CRP	N	N	DF	N	Def	N	5	6/60	**1.0**	6/18	**0.5**
N	Y	N	N	N	MVP, MR,AR,DF	N	N	N	10	6/60	**1.0**	6/6	**0.0**
Y	Y	N	TG	N	DF	N	N	N	-5	6/12	**0.3**	6/36	**0.8**
N	N	N	N	N	N	N	N	N	0	6/6	**0.0**	6/6	**0.0**
N	N	N	CHOL	N	DF	N	N	N	6	3/60	**1.3**	6/18	**0.5**
Y	Y	N	N	N	DF	N	N	N	3	6/18	**0.5**	6/9	**0.2**
Y	Y	N	LDL	N	DF	N	N	N	5	6/60	**1.0**	6/18	**0.5**
Y	Y	N	N	N	DF	N	N	N	4	6/24	**0.6**	6/9	**0.2**
Y	Y	N	Chol	N	DF	N	N	N	5	6/60	**1.0**	6/18	**0.5**
Y	Y	N	N	N	DF	N	N	N	MI	1/60	**1.8**	3/60	**1.3**
N	Y	N	Chol	N	MR, DF	N	N	N	4	6/24	**0.6**	6/9	**0.2**
Y	Y	N	TG,LDL	N	DF	N	N	N	6	6/36	**0.8**	6/9	**0.2**
N	Y	N	TG	N	DF	N	N	N	6	6/36	**0.8**	6/9	**0.2**

CRP Raised CRP levels, **FLP** Fasting Lipid Profile, **Chol, TG, HDL** Abnormal levels, **AR** Aortic Regurg, **MR** Mitral Regurg, **DF** Diastolic dysfunction, **MVP** Mitral Valve Prolapse, **IHD** Ischemic heart disease

DISCUSSION

Non Arteritic Anterior Ischemic Optic Neuropathy is the most common acute optic neuropathy. Multiple studies have shown the pathologic aetiology to be at the level of the circle of Zinn Haller. The resultant ischemic insult leads to loss of vision and optic disc swelling. This further compromises blood flow through the vessels. As mentioned previously the natural history of NAION does reveal a spontaneous improvement in vision in about 43% max. In our study, the percentage of patients improving was higher (67%). Three patients whose VA remained stable, presented with VA of 6/6. In this regard, being able to maintain their VA and avoid any loss was a further success. One of these three already had NAION in the fellow eye few months back, was managed in other centre and vision was severely impaired with optic atrophy in that eye. So, functionally he was one eyed and was complaining of the same sequence of symptoms, which in our view was the most important indication for starting him on treatment. Another patient who presented with a visual acuity of 6/6 had arterial sludging in retinal circulation and was found to be protein S deficient, hence was started on the therapy. Third patient with initial VA of 6/6 was diabetic and because of the presence of this risk factor it was decided to include him in our study.

Patients with marginal improvement of visual acuity had gross ONH ischemia at presentation and presented with severely reduced VA at presentation. The only patient in our study to suffer loss of 3 lines of vision despite anticoagulation therapy presented with VA of 6/12. At 1 month, VA had reduced to 3/60. However, at 6 months had had gained some improvement with VA on final follow-up of 6/36. None of our study patients developed NAION of the other eye during this study duration. In all our study patients we were able to achieve strict diabetic control (FBS <126 mg/dl; RBS <200 mg/dl) using multiple Insulin and (or) oral hypoglycaemic regimens. We were also successful in achieving blood pressure below range of 140/90 mmHg in all our study

patients. The limitations of our study include a small sample size, absence of a control group and not being able to exclude the possible beneficial effects of other factors like tight glycaemic and hypertensive control and intensive lipid lowering therapy when required. According to our calculations, the sample size required for this study to obtain results with 95% C.I and 10% chance of error is 312. The duration of anticoagulation therapy required also has to be established via a prolonged follow up. Also using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts would be a more scientific tool for recording of VA.

Any improvement and (or) stability of visual fields following anticoagulation therapy via repeated testing will also help improve the results of the study.

CONCLUSION

This pilot study might mark the beginning of a new era in the management of patients with Non Arteritic Anterior Ischemic Optic Neuropathy. Anticoagulation with Warfarin and Heparin does seem to be beneficial in patients with NA-AION presenting within 4 weeks of onset of symptoms.

The authors of this study propose a multicentre randomized control trial, where in a larger sample size would be available. Patients could be randomized in two groups;

- Anticoagulated and offered tight control of risk factors like diabetes, hypertension and hyperlipidaemia,
- Placebo group with management of risk factors only.

ACKNOWLEGMENT

We wish to acknowledge the advice and comments of Dr Robert McFazdean (Late) on the initial results.

AUTHORS' CONTRIBUTION

AMA: Collection of data, article writing. MI: Conceptualization of study, article writing. AR: Statistical analysis. AA: Data Collection, Proof reading

REFERENCES

1. Arnold AC. Ischemic optic neuropathy. In: Miller NR, Newman NJ, Biousse V, Kerrison JB, edotors. Walsh & Hoyt's Clinical Neuro-Ophthalmology, 6th ed. I. Philadelphia: Lippincott Williams & Wilkins; 2005. p.349–384.
2. Pahor A, Pahor D. [Clinical Findings in Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy (NA-AION) Under 50 Years of Age]. Klin Monbl Augenheilkd 2016;233(1):66–71.
3. Miller NR. Current concepts in the diagnosis, pathogenesis, and management of nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2011;31(2):e1–3.
4. Sohn BJ, Chun BY, Kwon JY. The effect of an intravitreal triamcinolone acetonide injection for acute nonarteritic anterior ischemic optic neuropathy. Korean J Ophthalmol 2009;23(1):59–61.
5. Wilhelm H, Beisse F, Ruther K. [Non-Arteritic Ischemic Optic Neuropathy (NAION)]. Klin Monbl Augenheilkd 2015;232(11):1260–9.
6. Neuro-ophthalmology: Optic nerve Anatomy. In: Kanski JJ, Bowling B, editors. Clinical Ophthalmology A systematic approach, 7th ed. New York, Elsevier Saunders; 2011. p.783–859.
7. Hiraoka M, Inoue K, Ninomiya T, Takada M. Ischaemia in the Zinn-Haller circle and glaucomatous optic neuropathy in macaque monkeys. Br J Ophthalmol 2012;96(4):597–603.
8. Acheson JF, Sanders MD. Coagulation abnormalities in ischaemic optic neuropathy. Eye (Lond) 1994;8(Pt 1):89–92.
9. Zotz RB, Finger C, Scharf RE, Unsold R. Associations between thrombophilic risk factors and determinants of atherosclerosis and inflammation in patients with non-arteritic anterior ischaemic optic neuropathy. Hamostaseologie 2016;36(1):46–54.
10. Yao F, Wan P, Su Y, Liao R, Zhu W. Impaired systemic vascular endothelial function in patients with non-arteritic anterior ischaemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol 2016;254(5):977–81.
11. Lacharme T, Almanjoumi A, Aptel F, Khayi H, Pepin JL, Baguet JP, *et al*. Twenty-four-hour rhythm of ocular perfusion pressure in non-arteritic anterior ischaemic optic neuropathy. Acta Ophthalmol 2014;92(5):e346–52.
12. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1994;118(6):766–80.
13. Andrew A Dahl. Anterior Ischemic Optic Neuropathy Clinical Presentation: History, Physical, Causes [Internet]. [cited 2015 April 2]. Available from: http://emedicine.medscape.com/article/1216891-clinical#a0218
14. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol 1994;117(5):603–24.
15. Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. Ophthalmologica 1999;213(2):76–96.
16. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: clinical characteristics in diabetic patients versus nondiabetic patients. Ophthalmology 2008;115(10):1818–25.
17. Hayreh S. Acute ischemic disorders of the optic nerve: pathogenesis, clinical manifestations, and management. Ophthalmol Clin N Am 1996;9:407–42.
18. Hayreh SS. Non-arteritic anterior ischemic optic neuropathy versus cerebral ischemic stroke. Graefes Arch Clin Exp Ophthalmol 2012;250(9):1255–60.
19. Hayreh SS. Non-arteritic anterior ischaemic optic neuropathy and phosphodiesterase-5 inhibitors. Br J Ophthalmol 2008;92(12):1577–80.
20. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. The Ischemic Optic Neuropathy Decompression Trial Research Group. JAMA 1995;273(8):625–32.

Received: 24 July, 2015	*Revised: 22 April, 2016*	*Accepted: 16 September, 2016*

Address for Correspondence:
Awais Rauf, Department of Ophthalmology, Khyber Teaching Hospital, Peshawar-Pakistan
Cell: +92 345 920 3306
Email: drawaisrauf@gmail.com