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NEUROPHTHALMOLOGY

Visual and anatomical outcomes of non-arteritic anterior ischemic optic neuropathy with high-dose systemic corticosteroids

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Abstract
Background To evaluate the visual and anatomic outcomes after systemic steroid treatment in non-arteritic anterior ischemic optic neuropathy (NAION).
Methods Ten eyes from ten patients diagnosed with NAION and treated during the acute phase with 80 mg daily, tapering-down dose of corticosteroids were compared with a non-contemporary cohort of 27 patients that received no treatment. The visual outcomes of treated and untreated group were compared. Patients underwent complete ophthalmic examination including determination of Snellen visual acuity (VA), visual fields (VFs) (standard automated perimetry, Swedish Interactive Testing Algorithm 24–2 strategy), and optical coherence tomography (OCT) scanning of the optic nerve head at diagnosis, 6–8 weeks and 6 months after presentation.
Results No statistical differences were found between steroid-treated and untreated NAION for the median change in VA (Mann–Whitney $P=0.28$), median change in VF mean deviation (MD) and median change in VF pattern standard deviation (PSD) (Mann–Whitney $P=0.213$ and $P=0.07$ respectively). Statistical analysis showed no differences when comparing average RNFL loss ($P=0.871$) and RNFL loss for superior, nasal, inferior and temporal optic disc quadrants between both groups. Complications occurred in three of the ten treated patients (30%); in one of them, steroid therapy had to be discontinued. Another two patients developed a NAION in their fellow eye after 2 and 3 months while on low-dose prednisone. No complications developed in the control group. The study was interrupted early due to a significantly higher rate of complications observed in the treated group ($P=0.002$)
Conclusion High-dose systemic steroid treatment did not show any beneficial effect in visual and anatomic outcomes when given during the acute phase of NAION. Furthermore, it caused serious complications in a third of the patients treated.

Keywords Non-arteritic anterior ischemic optic neuropathy · Steroids · Treatment · Outcomes

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Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is a sight-threatening entity characterized by the sudden onset of visual loss with ipsilateral optic nerve edema. Although its pathogenesis remains unclear, the current believe is that ischemia of the anterior part of the optic disc due to a transient hypoperfusion may precipitate a compartment syndrome of the optic nerve head (ONH) leading to clinical features of NAION [1]. Currently a number of therapies proposed for NAION treatment have shown controversial and inconsistent effects [2]. Efforts to improve blood flow to the optic nerve head during the acute phase [3–7] have been unsuccessful. Different neuroprotective strategies aimed at both improving neuronal survival and

limiting axonal injury have been proposed in NAION [8]. Disappointingly, systemic levodopa and carbidopa, topical brimonidine tartrate, and hyperbaric oxygen therapy failed to provide beneficial effect. Hayreh [9] recently reported a large retrospective non-randomized study which suggested that systemic corticosteroid therapy given during the acute phase of NAION significantly improved visual acuity (VA) and visual fields (VF). The non-randomized nature of the study, in which patients decided whether or not they were to receive treatment, and the higher prevalence of vascular risk factors in the untreated group makes it necessary to interpret these results with caution.

The aim of this study was to evaluate prospectively the effect of systemic corticosteroid therapy in acute NAION, and to compare the visual and anatomic outcomes with a non-contemporary cohort of patients with NAION who did not receive any treatment.

Material and methods

All patients diagnosed with NAION in the Hospital Ramón y Cajal (Madrid) between September 2008 and September 2009 were considered for inclusion. The diagnosis of NAION was based on the following criteria: (1) history of sudden visual loss in the absence of other ocular and neurologic disease that might explain the patient's visual symptoms, (2) optic disc edema, (3) visual field defects consistent with NAION, and (4) erythrocyte sedimentation rate and reactive protein C levels within normal values, with no signs or symptoms suggestive of giant cell arteritis. Patients were offered treatment with corticosteroids only if they consulted within 2 weeks after onset of visual loss. Patients with inflammatory, traumatic, demyelinating, infiltrative, or compressive causes of optic neuropathy were excluded. The presence of ocular pathology in the unaffected eye or previous cataract surgery in the affected eye were not exclusion criteria. Patients with any systemic condition which precluded treatment with systemic corticosteroid (limited cardiac reserve, severe immunosuppression or active tuberculosis) were not included. All participants gave their informed consent according to the Declaration of Helsinki.

At diagnosis, a detailed ophthalmic and medical history was obtained. Patients underwent a complete ophthalmological evaluation, including the assessment of Snellen VA, relative afferent papillary defect, intraocular pressure (IOP), slit-lamp examination of the anterior and posterior pole, VF with a Humphrey perimeter (Humphrey Systems, Dublin, CA, USA) Swedish Interactive Testing Algorithm (SITA) 24–2 strategy, and optical coherence tomography (OCT) scanning of the optic nerve head. Optical coherence tomography scanning was performed with both Stratus OCT (time-domain OCT) and Cirrus OCT (spectral-domain OCT) after pharmacological midriasis. All these examinations were repeated 6–8 weeks and 6 months after treatment, and whenever considered necessary during the treatment period (Fig. 1).

Treatment

All patients who fulfilled the inclusion and exclusion criteria were informed about the possible side effects of corticosteroid treatment, and all their questions were answered in an unbiased way. No patient rejected participation in the study. A detailed description of the treatment schedule was given to each patient so that their primary care physicians could monitor them closely for the duration of the study. The corticosteroid therapy protocol consisted in an initial dose of 80 mg of prednisolone (irrespective of their weight) daily taken during 2 weeks. After this period, tapering down of therapy was started in steps of 5 days each: to 70 mg, 60 mg and then cutting down by 5 mg every 5 days to 40 mg until the optic disc edema was resolved. After that, it was rapidly tapered off. Patients were on treatment for approximately 2–3 months. The patients were followed every 2 weeks as long as they were taking up to 40 mg prednisolone daily, and at 4-week intervals after that until therapy was stopped.

Statistical analysis

Statistical analyses were performed using SPSS software, version 16.0 (SPPS Inc.,Chicago, IL, USA). Before analysis, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) scale. Given the small sample size, nonparametric test were used. Mann–Whitney U test was used to compare VA, visual field defects and retinal nerve fibre layer thickness between the treated and untreated groups. A P value of 0.05 or less was considered significant.

Results

Ten patients (treated group) were treated with corticosteroid therapy (three women and seven men; median age 73.5 years [range 53 – 90]). Mean time from onset of visual loss to examination and treatment initiation was 5.1 ± 2.6 days. Seven patients had hypertension (70 %), one had diabetes mellitus (10 %) and one had hypercholesterolemia (10 %). All except one patient had at least one known vascular risk factor. Two patients had suffered a previous non-diagnosed NAION episode in their fellow eye that was discovered during the initial visit. One patient underwent cataract surgery 20 days before onset of NAION. One patient who had completed treatment with chemotherapy after breast cancer surgery 6 months before onset of NAION was included in the study after consultation with her oncologist. The corticosteroid therapy protocol as described above was completed by nine

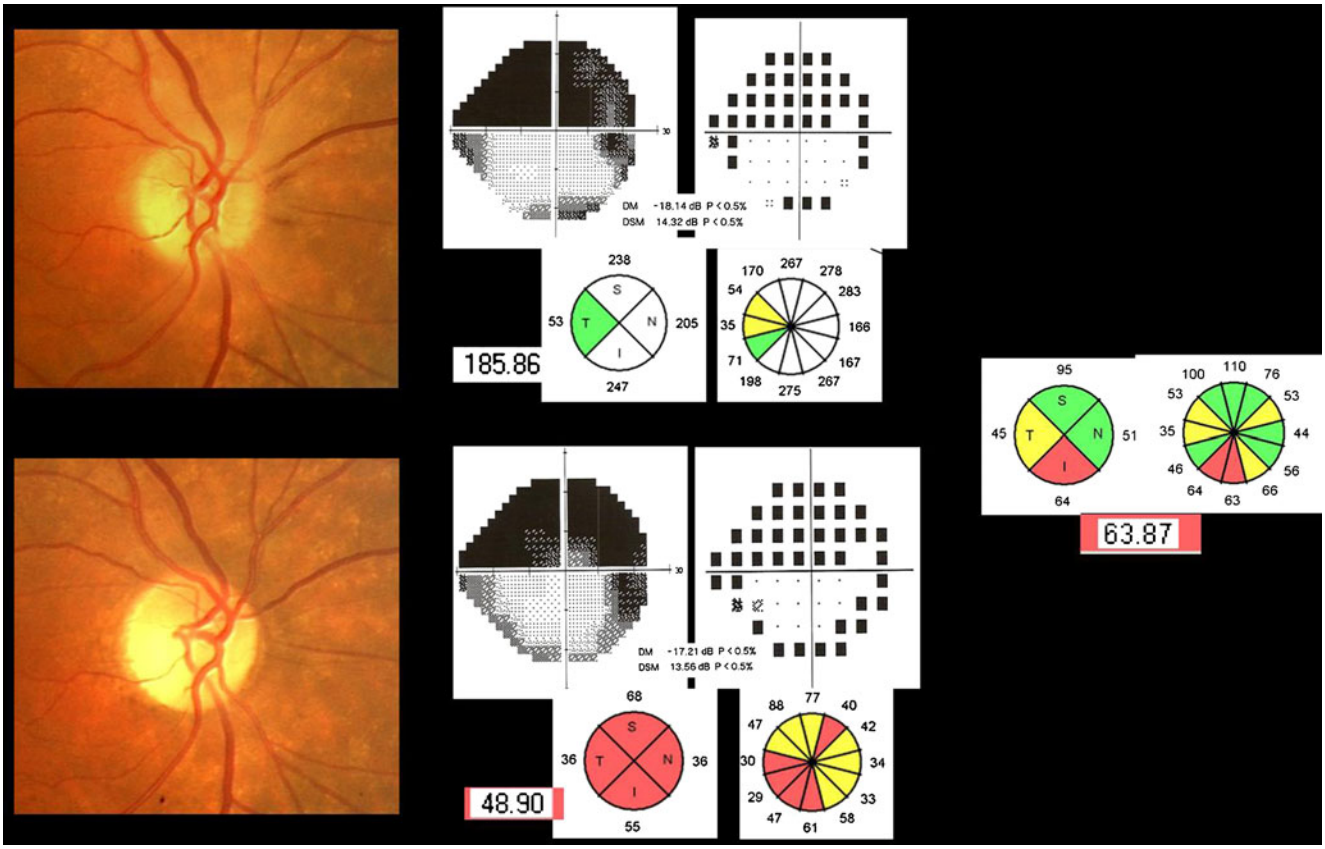

Fig. 1 Example of test results of optic disc photography, Humphrey visual field (VF) pattern deviation and Stratus-OCT peripapillary retinal nerve fibre layer (RNFL) thickness from a patient with non-arteritic ischemic optic neuropathy (NAION) and a superior altitudinal field defect. Acute NAION (baseline visit) and atrophic stage (6-month visit) are shown. Stratus-OCT peripapillary RNFL thickness measured at 2 months follow-up visit shows RNFL thinning in the inferior sector of the optic nerve

patients. In one patient, treatment was stopped when at a 40-mg daily dose due to severe secondary effects. This patient was excluded from the statistical analysis.

The control group included 27 patients diagnosed with NAION who received no treatment. The natural history of this cohort has already been reported in detail elsewhere [10].

Demographic characteristics of both the treated and untreated group are summarized in Table 1. Mean and median age of patients, time from onset to initial examination, and the presence of cardiovascular risk factors were similar in both groups. At diagnosis, diffuse optic disc swelling was the most common pattern of optic disc edema in both the treated group (70 %) and the untreated group (86.2 %). Differences in VA, VF defects and changes in RNFL between both groups are assessed at initial (baseline) and final visit (6-month follow-up).

Visual acuity

In the corticosteroid-treated group, median VA at presentation was 20/100, ranging from counting fingers to 20/15. Median change in logMAR VA between the initial and 6-month visit was −0.032 (SD 0.21). An improvement of 2 or more Snellen lines was found in one patient (1/9); in the other eight patients (8/9), VA remained stable (± 1 Snellen lines). The patient who stopped steroid treatment and was excluded from analysis suffered a visual acuity worsening of 2 Snellen lines while on treatment. In the cohort of untreated patients median initial VA was 20/50 (range from hand movements to 20/20). Median change in logMAR VA between initial and 6-month visits was 0.00 (SD 0.84). In 22.2 % of patients, VA improved≥2 Snellen lines, in 22.2% VA worsened≥2 Snellenlines, and VA remained stable in 55.6%. Statistical analysis did not show a significant difference in median change in VA between the treated and untreated groups (Mann–Whitney, P=0. 28). (Table 2)

Visual fields

In the corticosteroid-treated group, median VF mean deviation (MD) at presentation was −19.71 dB (SD 6.3), and

Table 1 Demographic and clinical characteristics of NAION patients included

	Steroid therapy group (n=10)	Untreated group (n=27)	P value
Age (median ± SD)	73.5 ± 11.6	68 ± 10.4	0.358
Gender (male)	70 %	51.7 %	
Involved eye			
Right eye	50 %	48.3 %	
Left eye	50 %	51.7 %	
Mean time from onset to examination (median days ± SD)	5.1 ± 2.6	5 ± 4.7	0.219
Systemic conditions			
Hypertension	70 %	55.6 %	0.48
Diabetes mellitus	10 %	11.1 %	1
Hypercholesterolemia	10 %	18.5 %	1
Aspirin use	20 %	17.2 %	

median VF pattern standard deviation (PSD) was 10.28 dB (SD 2.73). Visual field defects included: superior hemifield defects (20 %), inferior altitudinal defects (20 %), diffuse and severe VF loss (40 %), a peripheric defect (10 %) and a centrocecal scotoma (10 %). The patient that had to stop corticosteroids had an initial superior altitudinal VF defect which progressed to a severe diffuse defect within the first month of follow-up. In all other patients, VF defects remained stable. Median VF MD at the 6-month visit was −21.97 dB (SD 5.3) and median VF PSD was 11.7 dB (SD 2.69). Median change in MD was −0.56 dB (SD 5.03) and it was not statistically different compared to median change in MD in the untreated group (Mann–Whitney, P=0.213). Median change in PSD was not statistically different between treated and untreated patients (−0.02 and 0.91 respectively, P=0.07) (Table 2)

Retinal nerve fibre layer

Table 3 shows, for the study and control group, the median Stratus-OCT RNFL thickness values for all four optic disc quadrants and for the average RNFL thickness at onset and at the 6 month visit. No statistically significant differences were found in median average RNFL thickness at no time point between both groups (P=0.58 and P=0.706 respectively). After excluding from the analysis patients who had had a previous episode of NAION in their fellow eye and those who developed a new event in the unaffected eye during follow-up, median RNFL loss 6 months after onset, compared to the patient's unaffected fellow eye, was of 37.20 ± 15.48 μm for the corticosteroid-treated group and 44.53 ± 20.09 μm in for the control group (P=0.554). No differences were found when comparing average RNFL loss between both groups; RNFL loss for the superior, nasal, inferior, and temporal sectors was also similar between both groups (P=0.871, P=0.903, P=0.655, P=0.273 and P=0.394 respectively).

Complications

Among the ten patients who were recruited for the corticosteroid therapy protocol group, three (30 %) developed systemic complications during the 6-month follow-up period. One patient, who had no previous psychiatric history, suffered a prednisone-induced depression that required the discontinuation of treatment. A patient with diabetes mellitus controlled with oral therapy had to start on insulin to control her blood glucose levels while on treatment, and had to remain on

Table 2 Clinical features (median ± standard deviation and interquartile range P25–P75 [IQR]) of NAION eyes at the initial and 6-month examination

	Steroid therapy group (n=9)	Untreated group (n=27)	P value
Visual acuity onset (logMAR)	0.69 (±0.57) [0.34; 1.07]	0.4 (±0.82) [0.18;0.9]	0.173
Median change VA	−0.032 (±0.21) [−0.3; 0.04]	0.00 (±0.84) [−0.14; 0.52]	0.28
MD onset (dB)	−19.7(±6.3) [−23.7; −12.9]	−17.4 (±6.9) [−26.3; −15.5]	0.874
MD 6 months (dB)	−21.9 (±5.3) [−24.8; −15.2]	−18.4 (±4.6) [−26.1; −10.6]	1.00
Change MD (final–initial)	−0.56 (±5.03) [−3.6; 0.7]	1.27 (±6.9) [−2.14; 5.2]	0.213
PSD onset (dB)	10.3 (±2.7) [7.7; 12.9]	11.8 (±4.2) [7.7; 13.2]	0.548
PSD 6 months (dB)	11.7 (±2.7) [8.5; 12.8]	9.3 (±4.1) [7.1; 11.7]	0.213
Change PSD (initial–final)	−0.02 (±1.9) [−1.6; 0.6]	0.91 (±4.8) [−0.75; 2.9]	0.07

CF, counting fingers; HM, hand motion; MD, mean deviation; PSD, pattern standard deviation; * P values for Mann–Whitney test

Table 3 Average and quadrant retinal nerve fibre layer (RNFL) thickness at the initial and 6-month examination (median ± standard deviation and interquartile range P25–P75 [IQR])

	Steroid therapy group (n= 9)	Untreated group (n=27)	P value
RNFL thickness onset			
Average	207.6 (±58.7) [177.6; 265.1]	189.2 (±51.8) [155.2; 238]	0.580
Superior	251 (±81.3) [164.2; 291]	228 (±86.7) [174.5; 281.5]	0.685
Nasal	172.5 (±83.1) [125.7; 220.7]	175 (±70) [108; 225]	0.825
Inferior	281 (±42.5) [252; 316.7]	216 (±75.4) [165.5; 296.5]	0.06
Temporal	170.5 (±68.2) [87.2; 207.5]	178 (±76.3) [105; 248]	0.406
RNFL thickness 6 months			
Average	57.9 (±12.5) [48.6; 67.9]	54.3 (±17.3) [47.2; 65.7]	0.763
Superior	66 (±13.1) [46; 71]	56 (±26.2) [42; 70]	0.546
Nasal	47 (±11.6) [36.5; 58.5]	53 (±20.3) [38.2; 62.2]	0.508
Inferior	85 (±36.3) [55; 120]	70.5 (±29.8) [54.2; 82]	0.438
Temporal	40 (±9.9) [32; 51]	40 (±15.4) [34.5; 49]	0.910
Difference RNFL thickness (onset–final)			
Average	150.5 (± 64.9) [119.8; 212.7]	148,5 (±55.7) [103.6; 188]	0.871
Superior	184 (±79.7) [113.2; 228.7]	163 (±80.2) [116; 229]	0.903
Nasal	116 (±87.9) [76; 184]	127 (±74.9) [60; 171.2]	0.655
Inferior	209.5 (±71.6) [154; 260]	150 (±87.8) [72.5; 211.2]	0.273
Temporal	130 (±73.1) [35.2; 179.5]	145 (±79.7) [56.7; 211.5]	0.394

RNFL DIF: RNFL thickness onset–RNFL final examination (measured with Stratus-OCT).; * P values for Mann– Whitney test

insulin even after completing the steroid treatment. A third patient developed a bilateral pulmonary embolism 6 weeks after the onset of NAION. Steroid treatment was not interrupted, as it was presumably not related to the episode and the patient was tapering off treatment. Two further patients needed topical medication to control steroid-induced ocular hypertension while on treatment. In one of them, the IOP elevation was not reversible despite cessation of steroid use.

Two patients developed a NAION in their fellow, previously unaffected eye, 2 and 3 months respectively after the initial diagnosis of NAION.

In the group of patients who received no treatment, no complication was reported during the 6 months of follow-up (Mann–Whitney test P=0.002).

Discussion

Up to now, there is no generally accepted treatment for NAION, although several medical and surgical therapies have been proposed [2]. Hayreh and other authors have described the use of systemic steroids as a useful therapy to improve visual outcomes in NAION [9, 11, 12]. This study was designed to compare the outcomes of patients treated with oral corticosteroid with a non-contemporary, prospectively studied untreated cohort of patients with NAION.

In our study, corticosteroid- treated patients did not show a better VA and VF outcome than patients in the untreated group. No statistically significant differences were found when comparing initial VA, 6-month VA or VA change between both groups. Moreover, the control group showed a median MD improvement of 1.27 dB, while the steroid-treated group showed a median MD worsening of 0.56 dB, although this difference was not statistically significant.

Hayreh [9] reported an improvement of VA in 70 % of patients treated with systemic steroids within 2 weeks from onset with an initial VA of 20/70 or worse, compared to an improvement in VA in only 13 % of patients with an initial VA of 20/60 or better. In a previous publication, Hayreh [12] had reported an improvement in VA in 75 % of eight treated patients compared to 17 % of six untreated eyes. In our study, of the ten patients included in the steroid-therapy group, eight patients had an initial VA≤20/70, and showed no improvement in their VA after corticosteroid treatment. Of the other two patients, one patient was excluded from analysis because of a major complication while on treatment (as discussed above), but during the 2 weeks he received treatment his VA decreased 2 Snellen lines. In the other patient, VA improved to 20/30.

In Hayreh's cohort of treated patients, visual field defects graded as moderate to severe showed an improvement in 40 % of patients, while in our steroid-treated group no significant change in VF defects was registered 6 months after diagnosis. In the untreated patients, VF MD did not differ significantly from onset to the last visit; VF PSD, however, did improve significantly (P=0.048).

Thus, our results did not show a beneficial effect of systemic steroid therapy on the visual outcomes after NAION. Moreover, three major complications occurred in the first 2 months of corticosteroid treatment. In one case, it was

necessary to stop prednisone therapy due to a severe depression. However, in Hayreh's cohort (n=364) treatment was not stopped in any case.

Cohort and population-based studies have established that there is a cumulative probability of 25 % to 15 % of developing NAION in the initially unaffected eye during the first 3 to 5 years after onset, with an increased incidence in patients with poor baseline visual acuity or diabetes mellitus [1, 13]. In our combined cohort, two patients (2/35; 5.71 %) developed a NAION in their fellow eye during the six-month follow-up period, both included in the treatment group (2/9; 22.2 %) while on a low dose of prednisone. In the untreated group, one patient (1/27) developed fellow eye NAION after 12 months of follow-up.

The RNFL thickness measurements obtained with Stratus OCT were used as an objective tool for evaluating the effect of corticosteroids. No significant differences were found in RNFL thickness loss between treated and untreated patients or in average thickness ,in the superior, nasal, inferior or temporal quadrants (Table 3). There was no difference in RNFL thickness loss between two groups when comparing the affected and fellow eye. Thus, no benefit of steroid treatment in RNFL thickness changes was found.

The main limitation of our study is the small number of patients included in the treated group. This is due to the premature interruption of the study prompted by the unexpectedly statistically significant higher rate of complications observed in the treated group. Another flaw is that patients were not randomized to receive or not receive treatment; during the study period, corticosteroids were suggested to all patients diagnosed with NAION. Despite this limitation, our study did not show any beneficial effect (neither visual nor anatomic) of systemic steroid therapy when given during the acute phase of NAION. On the other hand, it may lead to serious complications. In addition, our results suggest that corticosteroid treatment could predispose to the development of NAION in fellow eyes with a disk "at risk".

Conflict of interest Authors disclose no financial interest.

References

1. Hayreh SS (2009) Ischemic optic neuropathy. Prog Retin Eye Res 28(1):34–62
2. Atkins E, Bruce B, Newman N, Biousse V (2010) Treatment of nonarteritic anterior ischemic optic neuropathy. Surv Ophthalmol 55:47–63
3. Bonamour G (1966) Apropos de pseudo-papillites vasculaire. Bull Soc Ophtalmol Fr 79:846
4. Georgiades G, Konstas P, Stangos N (1966) Reflexions issues de l'etude de nombreaux cas de pseudo-papillite vasculaire. Bull Soc Ophtalmol Fr 79:506–536
5. Haas A, Walzl M, Jesenik F, Walzl B, Berghold A, Berglöff J, Feigl B, Faulborn J (1997) Application of HELP in nonarteritic anterior ischemic optic neuropathy: a prospective, randomized, controlled study. Graefes Arch Clin Exp Ophthalmol 235(1):14–19
6. Kajiwara K, Tsubota K, Hara Y (1990) High dose urokinase thrombolysis and stellate ganglion block for anterior ischemic neuropathy. Fola Ophthalmol Jpn 41(1):59–64
7. Kollarits CR, McCarthy RW, Corrie WS, Swann ER (1981) Norepinephrine therapy of ischemic optic neuropathy. J Clin Neuro-ophthalmol 1(4):283–288
8. Levin LA (2007) Axonal loss and neuroprotection in optic neuropathies. Can J Ophthalmol 42(3):403–408
9. Hayreh SS, Zimmerman MB (2008) Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. Graefes Arch Clin Exp Ophthalmol 246(7):1029–1046
10. Contreras I, Noval S, Rebolleda G, Muñoz-Negrete FJ (2007) Follow-up of nonarteritic anterior ischemic optic neuropathy with optical coherence tomography. Ophthalmology 114(12):2338–2344
11. Foulds WS (1970) Visual disturbances in systemic disorders: optic neuropathy and systemic disease. Trans Ophthalmol Soc UK 89:125–146
12. Hayreh SS (1974) Anterior ischaemic optic neuropathy. III. Treatment, prophylaxis, and differential diagnosis. Br J Ophthalmol 58 (12):981–989
13. Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D, Dickersin K, Ischemic Optic Neuropathy Decompression Trial Research Group (2002) The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. Am J Ophthalmol 134(3):317–328