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Review Article

Treatment strategy for non-arteritic anterior ischemic optic neuropathy

Tzu-Lun Huang [a,b], Kung-Hung Lin [c], Rong-Kung Tsai [a,b,*]

[a] Department of Ophthalmology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[b] Department of Ophthalmology and Visual Science, Tzu Chi University, Hualien, Taiwan
[c] Department of Neurology, Taiwan Adventist Hospital, Taipei, Taiwan

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ABSTRACT

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of sudden optic nerve (ON)-related visual loss in persons over the age of 55. The pathogenesis is still unclear and no effective treatment has been established. The possible pathway is a vicious cycle of ischemia causing consequential compartment syndrome at the optic nerve head, resulting in further ischemia and optic nerve fiber infarction. Many medical and surgical interventions aim to shorten the duration of disk edema. The Ischemic Optic Neuropathy Decompression Trial (INODT) was the only level I evidence of treatment trial but it ended in failure. The use of steroids for acute NAION is still controversial. Several clinical case-serial reports showed some benefits. A recently developed animal model of anterior ischemic optic neuropathy may provide valuable preclinical data for both drug testing and treatment strategies.

1. Introduction

In adults, anterior ischemic optic neuropathy (AION) is the second most common cause of optic nerve-related visual impairment after glaucoma [1]. AION includes nonarteritic, arteritic and perioperative types. Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common type of AION. The pathogenesis and treatment of NAION is an interesting and controversial topic. Implicated causative factors include nocturnal hypotension, impaired autoregulation of the microvascular supply, vasculopathic occlusion, and venous insufficiency [2]. Although NAION is a disease of presumable microvascular ischemia at the paraoptic branches of the short posterior ciliary arteries, there is no thrombotic evidence or any systemic disorder tightly associated with NAION except for diabetes mellitus [3,4]. Patients with NAION clinically present with painless blurry vision associated with pallid swelling and hemorrhage of the optic disc, resulting in retinal ganglion cells apoptosis and permanent vision loss [5]. The most common pattern of visual field defect is an altitudinal defect, and about two thirds of the visual field defect is a lower altitudinal visual field defect (Fig. 1).

Acute disk edema in NAION may contribute to further axonal damage via a vicious cycle of ischemia causing edema and compartment syndrome, so medical and surgical interventions aim to shorten the duration of disk edema to prevent further axonal ischemia to decrease neuron death [6,7]. However, there is no generally accepted treatment for NAION. We review and summarize medical and surgical therapies being reported in the literature based on the level of evidence [8].

2. Assessment of level of evidence

We classified recent clinical studies of NAION treatment based on the Oxford Centre for Evidence-Based Medicine - levels of evidence [8] (Table 1). We reviewed all published reports on the treatment of NAION since 1990. Most associated studies are case reports, case series and case controlled studies (Level IV and III). The only class I trial for NAION was the Ischemic Optic Neuropathy Decompression Trial (IONDT) in 1995 [9] (Table 2).

3. Treatment of acute NAION

3.1. Systemic and local treatment with corticosteroids

The rationale for the use of steroids in NAION comes from the postulation that steroids decrease capillary permeability, thereby inducing faster resolution of disk edema. Although there is no proven treatment for NAION, 10 % of physicians in the USA choose

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* Corresponding author. Department of Ophthalmology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 8561825x2112; fax: +886 3 8577161.
E-mail address: rktsai@tzuchi.com.tw (R.-K. Tsai).

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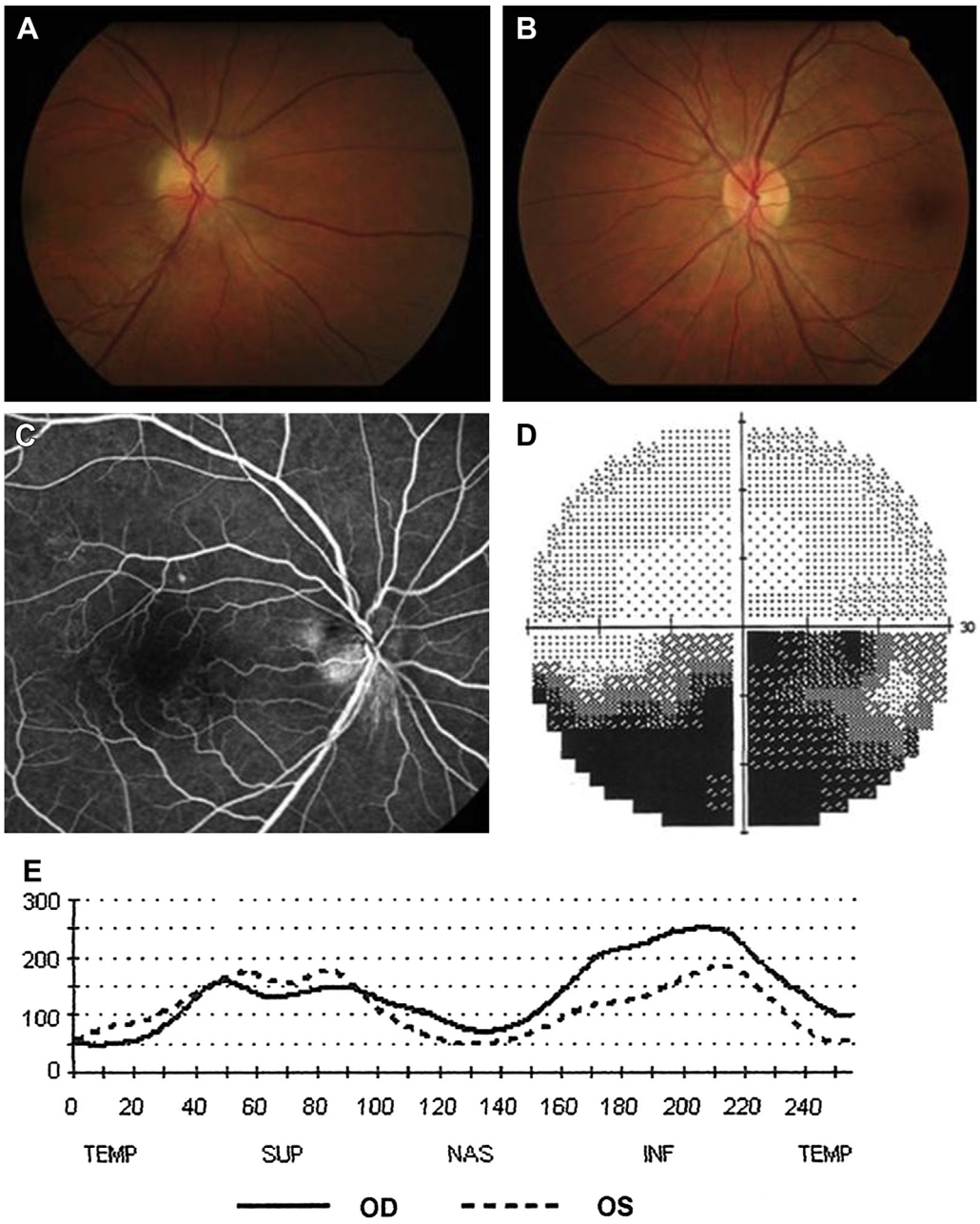

Fig. 1. (A) Fundus photographs of a right eye with optic disc edema during the the active phase of NAION. (B) Normal disc in the left eye of the same patient. (C) Fluorescein fundus angiogram of the eye with NAION showing a relatively dark part of the disc (ischemic area in the upper half of the disc) and reactive hyperemia with dye leak in the disc (edema area in the lower half of the disc). (D) Typical inferior altitudinal visual field defect correlated with an ischemia lesion in the upper part of the optic disc. (E) Optic coherence tomography demonstrating that circumpapillary nerve fiber layer thickness shows obvious fiber thinning in the superior sector and thickening in the inferior sector of the right optic nerve (solid line) compared with a normal symmetric double hump pattern in the left optic nerve fiber layer (dotted line). INF = inferior; NAS = nasal; OD = oculus dexter; OS = oculus sinister; SUP = superior; TEMP = temporal.

oral steroids and 19% choose high dose intravenous pulse steroid therapy [10]. A retrospective study by Hayreh and Zimmerman showed that systemic steroid treatment was effective in patients with NAION who had an initial visual acuity 20/70 or worse and were seen within 2 weeks of onset [11]. However, their patients were not randomized, and the untreated group had more vascular risk factors, making it hard to interpret whether oral steroids is a treatment of choice in NAION (Level III) [11–13]. Moreover, a recent study in ten patients with NAION showed that high-dose systemic steroid (oral prednisolone 80 mg/day) treatment did not show any beneficial effects in NAION, and three treated patients even had complications caused by steroid application [14]. These controversial results can be explained by a high spontaneous improvement rate in NAION (41%) and a broad spectrum of clinical presentations. These variable clinical manifestations of NAION not only easily bias clinical studies, but cause difficulty in designing a prospective study [9,15]. The rationale for intravitreal injection of steroids is the same as for systemic steroids. In clinical practice, intravitreal injection of triamcinolone acetonide (TA, 4 mg) is routinely used to treat retinal edema in conditions such as diabetic retinopathy or retinal vascular occlusion [16–18]. However, only case controlled report [19] (Level III) and case series [20,21] (Level IV) applied local intravitreal injection of TA in NAION. The results were inconclusive though some patients had visual improvement

Table 1
Level of evidence and type of study.

Level I: Systematic review of randomized trials (RT) and high quality RT (e.g., > 80% follow up, narrow confidence interval)
Level II: Systematic review of cohort studies, lesser quality RT (e.g., <80% follow up, wide confidence interval, no clear randomization, problems with blinding), individual cohort study; including matched cohort studies (prospective comparative studies), ecological studies
Level III: Systematic review of case-control studies, individual case-control study
Level IV: Case-series, poor quality cohort and case-control studies
Level V: Expert opinion

This chart is modified from material published by the Center for Evidence-Based medicine, Oxford, UK. March 2009.

[19–21]. We need prospective, randomized clinical trials to test the effects of TA and further concerns about intraocular pressure elevation after TA injection.

3.2. Intravitreal anti-vascular endothelial growth factor agents (anti-VEGF)

VEGF is a signal protein that stimulates angiogenesis and increases microvascular permeability. Anti-VEGF agents such as bevacizumab and ranibizumab inhibit the signaling of VEGF, thereby potentially decreasing optic disk edema [7]. In recent clinical applications, anti-VEGF agents were routinely used in age-related neovascular macular degeneration and in macular edema associated with other retinal vascular disorders. Prescott et al. concluded that anti-VEGF therapy has no beneficial effects in NAION [22]. However, bevacizumab treatment in NAION was limited to one case report and one case series (Level IV), with only one patient got visual improvement [22,23]. A case report of another anti-VEGF agent, ranibizumab, concluded it was effective in reducing optic nerve swelling but there was no improvement in visual acuity (Level IV) [24]. Intravitreal anti-VEGF therapy for NAION requires further research to explore the potential vasoconstrictor effects and the stress on the cardiovascular system [25]. A preclinical trial in animal models or a randomized clinical trial may determine the role of anti-VEGF in NAION.

3.3. Aspirin

Only one study evaluated aspirin use and concluded that aspirin did not improve the visual outcome of NAION [26]. There was no benefit from reducing the risk of development of NAION in the fellow eye after taking aspirin [27]. However, other reports showed that aspirin reduced the incidence of NAION in a second eye [28,29]. Aspirin treatment failed because NAION is a hypotensive disorder, not a thromboembolic disorder [15].

3.4. Other neuroprotective agents

Other interesting treatments for NAION in the past decade involved neuroprotection. Disappointingly, levodopa and carbidopa failed to provide beneficial effects in NAION. In a prospective, double-masked, placebo controlled trial, brimonidine tartrate 0.2% eyedrops showed no therapeutic effects in patients with acute NAION (Level 1, 36 patients) [30]. Intravitreal injection of erythropoietin seemed to be effective (Level IV, 31 cases without control group). Twenty-seven eyes had visual acuity improvement (87%) at 6 months of follow up but there was no improvement in the visual field [31]. However, this study did not have a control group to strengthen its significance.

3.5. The Ischemic Optic Neuropathy Decompression Trial (IONDT)

In 1989, Sergott et al. reported optic nerve decompression improved the progressive form of NAION in a case serial report [32]. This report brought on worldwide debate. To resolve this issue, a multicenter-trial was developed. The Ischemic Optic Neuropathy Decompression Trial (IONDT), a randomized, single-blind, multicenter trial assessed the safety and efficacy of optic nerve decompression in cases of acute onset of NAION (Level 1, 258 patients). A window was made in the optic nerve sheath surrounding the optic nerve and theoretically releasing the pressure surrounding the optic nerve to relieve compartment syndrome. The IONDT found that surgery for NAION was not only ineffective, but could be harmful, and the trial was stopped early [9]. A database review in 2012 also indicated no evidence of a beneficial effect of surgery for NAION [33].

4. Using an animal model of NAION to investigate pathogenesis and drug efficacy

No effective, standard treatment for NAION has been reported in the literature. A prospective, randomized clinical trial is difficult to

Table 2
Summary of studies on the treatment of NAION.

Author (Year)	Level of evidence	Type of study	Treatment (Dose)	Outcome
Botelho (1996) [26]	III	Retrospective case control	Aspirin	No VA or VF improvement
Johnson (2000) [42]	III	Retrospective	Levodopa (100 mg levodopa/25 mg carbidopa 3 times daily)	VA improvement in 77% treated/30% of untreated
Wilhelm (2006) [30]	II	Randomized controlled	Brimonidine 0.2%	No VA or VF improvement
Modarres (2011) [31]	III	Prospective cases series	Intravitreal injection of 2000 unit of erythropoietin	VA improvement in 61.2% treated, no VF improvement
IONDT (1995) [9]	I	Randomized controlled	Optic nerve sheath decompression	No difference in VA outcome and more surgical patients worsened
Hayreh (2008) [11]	III	Nonrandomized controlled	Oral prednisone (80 mg tapering dose)	VA improvement in 69.8% treated/40.5% untreated; VF improvement in 40.1% treated/24.5% untreated
Kaderli (2007) [19]	III	Case control	Intravitreal triamcinolone (4 mg)	VA improvement in treated group
Jonas (2007) [20]	IV	Cases series	Intravitreal triamcinolone (20 mg)	No VA improvement
Bennett (2007) [23]	IV	1 total Case report	Intravitreal bevacizumab (1.25 mg/0.05 mL)	VA and disc swelling improve
Prescott (2012) [22]	IV	Case series	Intravitreal bevacizumab (1.25 mg/0.05 mL)	No effect on VA and VF
Pece (2010) [24]	IV	Case series	Intravitreal ranibizumab (0.5 mg/0.05 mL)	Reducing optic nerve swelling, no functional improvement

IONDT = Ischemic Optic Neuropathy Decompression Trial; NAION = nonarteritic anterior ischemic optic neuropathy; VA = visual acuity; VF = visual fields.

design because of the broad spectrum of disease severity and a spontaneous visual improvement rate of about 40% without treatment.

Recently, primate and rodent models of AION (rAION) have been developed and the mechanism of ischemic optic neuropathy has been studied [34–39]. To create a rAION model, a photodynamic application using both a photosensitizing agent and laser was developed [39]. The preferred model involves inducing transient coagulopathy, and the severity of the ischemic area can be adjusted by laser. After injection of a photosensitizing agent (Rose bengal [RB; Sigma-Aldrich (St.Louis, USA)]) through the tail vein, an argon-green laser light was aimed at the optic disc of the animals. This procedure creates photothrombosis on the vascular endothelium with both laser and RB applications. The rAION model is different than a central retinal vein occlusion (CRVO) model. The unit energy of a CRVO is higher and the laser time is longer (>25 s) than in the AION model and the target is the retinal veins near the optic head [40,41].

The method used to create AION in animal models may be quite different from the pathogenesis of human NAION [39]. The rAION model nevertheless provides a platform on which to test several potential treatments and illustrate the pathogenesis of NAION. The results of preclinical trials in the rAION model may bring us evidence to translate into new clinical trials for NAION.

5. Conclusion

NAION remains pathophysiologically unclear, and possible factors are vasculopathic occlusion or venous insufficiency impairing the autoregulation of microvascularity around the optic disc. Controversial treatments remain in the literature. Potential strategies for the future treatment of NAION should aim to avoid compartment syndrome to decrease secondary damage to axons, protect retinal ganglion cells from death (anti-apoptosis) and even use of regenerative medicine such as stem cell therapy.

References

[1] Miller NR. Current concepts in the diagnosis, pathogenesis, and management of nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2011; 31:e1–3.
[2] Kerr NM, Chew SS, Danesh-Meyer HV. Non-arteritic anterior ischaemic optic neuropathy: a review and update. J Clin Neurosci 2009;16:994–1000.
[3] Lessell S. Nonarteritic anterior ischemic optic neuropathy: enigma variations. Arch Ophthalmol 1999;117:386–8.
[4] Arnold AC, Badr MA, Hepler RS. Fluorescein angiography in nonischemic optic disc edema. Arch Ophthalmol 1996;114:293–8.
[5] Levin LA, Louhab A. Apoptosis of retinal ganglion cells in anterior ischemic optic neuropathy. Arch Ophthalmol 1996;114:488–91.
[6] Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of nonarteritic anterior ischemic optic neuropathy. Surv Ophthalmol 2010;55:47–63.
[7] Kelman SE. Intravitreal triamcinolone or bevacizumab for nonarteritic anterior ischemic optic neuropathy: do they merit further study? J Neuroophthalmol 2007;27:161–3.
[8] Oxford Centre for Evidence-based Medicine: Levels of Evidence. Available at: http://www.cebm.net/index.aspx?o=1025. Accessed March 2009.
[9] Smith DB. Ischemic optic neuropathy decompression trial. JAMA 1995; 274:612.
[10] Atkins EJ, Bruce BB, Newman NJ, Biousse V. Translation of clinical studies to clinical practice: survey on the treatment of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 2009;148:809.
[11] Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. Graefes Arch Clin Exp Ophthalmol 2008;246:1029–46.
[12] Hayreh SS. Non-arteritic anterior ischemic optic neuropathy and thrombophilia. Graefes Arch Clin Exp Ophthalmol 2009;247:577–81.
[13] Hayreh SS. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. Surv Ophthalmol 2010;55:399–400. author reply 400–01.
[14] Rebolleda G, Perez-Lopez M, Casas-Llera P, Contreras I, Munoz-Negrete FJ. Visual and anatomical outcomes of non-arteritic anterior ischemic optic neuropathy with high-dose systemic corticosteroids. Graefes Arch Clin Exp Ophthalmol 2013;251:255–60.
[15] Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: natural history of visual outcome. Ophthalmology 2008;115. 298–305 e2.
[16] Grover D, Li TJ, Chong CC. Intravitreal steroids for macular edema in diabetes. Cochrane Database Syst Rev 2008; CD005656.
[17] Johnson KS, Chu DS. Evaluation of sub-Tenon triamcinolone acetonide injections in the treatment of scleritis. Am J Ophthalmol 2010;149:77–81.
[18] Shields CL, Demirci H, Marr BP, Mashayekhi A, Dai VV, Materin MA, et al. Intravitreal triamcinolone acetonide for acute radiation papillopathy. Retina 2006;26:537–44.
[19] Kaderli B, Avci R, Yucel A, Guler K, Gelisken O. Intravitreal triamcinolone improves recovery of visual acuity in nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2007;27:164–8.
[20] Jonas JB, Spandau UH, Harder B, Sauder G. Intravitreal triamcinolone acetonide for treatment of acute nonarteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol 2007;245:749–50.
[21] 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;23:59–61.
[22] Prescott CR, Sklar CA, Lesser RL, Adelman RA. Is intravitreal bevacizumab an effective treatment option for nonarteritic anterior ischemic optic neuropathy? J Neuroophthalmol 2012;32:51–3.
[23] Bennett JL, Thomas S, Olson JL, Mandava N. Treatment of nonarteritic anterior ischemic optic neuropathy with intravitreal bevacizumab. J Neuroophthalmol 2007;27:238–40.
[24] Pece A, Querques G, Quinto A, Isola V. Intravitreal ranibizumab injection for nonarteritic ischemic optic neuropathy. J Ocul Pharmacol Ther 2010;26: 523–7.
[25] Mansour AM, Schwartz SG, Gregori NZ, Yehoshua Z, Freund KB, Dellatorre K, et al. Insight into 8 patients with nonarteritic anterior ischemic optic neuropathy following anti-VEGF injections. J Neuroophthalmol 2012; 32:193.
[26] Botelho PJ, Johnson LN, Arnold AC. The effect of aspirin on the visual outcome of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1996; 121:450–1.
[27] Beck RW, Hayreh SS, Podhajsky PA, Tan ES, Moke PS. Aspirin therapy in nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1997;123: 212–7.
[28] Salomon O, Rosenberg N, Steinberg DM, Huna-Baron R, Moisseiev J, Dardik R, et al. Nonarteritic anterior ischemic optic neuropathy is associated with a specific platelet polymorphism located on the glycoprotein Ibalpha gene. Ophthalmology 2004;111:184–8.
[29] Kupersmith MJ, Frohman L, Sanderson M, Jacobs J, Hirschfeld J, Ku C, et al. Aspirin reduces the incidence of second eye NAION: a retrospective study. J Neuroophthalmol 1997;17:250–3.
[30] Wilhelm B, Ludtke H, Wilhelm H. Efficacy and tolerability of 0.2% brimonidine tartrate for the treatment of acute non-arteritic anterior ischemic optic neuropathy (NAION): a 3-month, double-masked, randomised, placebo-controlled trial. Graefes Arch Clin Exp Ophthalmol 2006;244:551–8.
[31] Modarres M, Falavarjani KG, Nazari H, Sanjari MS, Aghamohammadi F, Homaii M, et al. Intravitreal erythropoietin injection for the treatment of non-arteritic anterior ischaemic optic neuropathy. Br J Ophthalmol 2011;95: 992–5.
[32] Sergott RC, Cohen MS, Bosley TM, Savino PJ. Optic nerve decompression may improve the progressive form of nonarteritic ischemic optic neuropathy. Arch Ophthalmol 1989;107:1743–54.
[33] Dickersin K, Manheimer E, Li T. Surgery for nonarteritic anterior ischemic optic neuropathy. Cochrane Database Syst Rev 2012;1: CD001538.
[34] Zhang C, Guo Y, Slater BJ, Miller NR, Bernstein SL. Axonal degeneration, regeneration and ganglion cell death in a rodent model of anterior ischemic optic neuropathy (rAION). Exp Eye Res 2010;91:286–92.
[35] Slater BJ, Mehrabian Z, Guo Y, Hunter A, Bernstein SL. Rodent anterior ischemic optic neuropathy (rAION) induces regional retinal ganglion cell apoptosis with a unique temporal pattern. Invest Ophthalmol Vis Sci 2008;49: 3671–6.
[36] Goldenberg-Cohen N, Guo Y, Margolis F, Cohen Y, Miller NR, Bernstein SL. Oligodendrocyte dysfunction after induction of experimental anterior optic nerve ischemia. Invest Ophthalmol Vis Sci 2005;46:2716–25.
[37] Danylkova NO, Alcala SR, Pomeranz HD, McLoon LK. Neuroprotective effects of brimonidine treatment in a rodent model of ischemic optic neuropathy. Exp Eye Res 2007;84:293–301.
[38] Chen CS, Johnson MA, Flower RA, Slater BJ, Miller NR, Bernstein SL. A primate model of nonarteritic anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci 2008;49:2985–92.
[39] Bernstein SL, Guo Y, Kelman SE, Flower RW, Johnson MA. Functional and cellular responses in a novel rodent model of anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci 2003;44:4153–62.
[40] Saito Y, Park L, Skolik SA, Alfaro DV, Chaudhry NA, Barnstable CJ, et al. Experimental preretinal neovascularization by laser-induced venous thrombosis in rats. Curr Eye Res 1997;16:26–33.
[41] Rehak M, Hollborn M, Iandiev I, Pannicke T, Karl A, Wurm A, et al. Retinal gene expression and Muller cell responses after branch retinal vein occlusion in the rat. Invest Ophthalmol Vis Sci 2009;50:2359–67.
[42] Johnson LN, Guy ME, Krohel GB, Madsen RW. Levodopa may improve vision loss in recent-onset, nonarteritic anterior ischemic optic neuropathy. Ophthalmology 2000;107:521–6.