Bilateral Posterior Ischemic Optic Neuropathy Associated With Use of Sildenafil

We report a case of sequential posterior ischemic optic neuropathy after the use of sildenafil.

A 76-year-old man with a history of systemic hypertension, hyperlipidemia, and stroke presented to our clinic with the sudden onset of sequential visual loss in his eyes. His usual medications were 50 mg atenolol daily and 90 mg diltiazem daily for hypertension and 10 mg simvastatin daily for hyperlipidemia. In addition, he had started taking a Chinese "health product" 7 weeks earlier. His usual dose was one capsule once a day or one capsule every other day, but he had stopped it 20 days earlier until 2 days before presentation, when he consumed three capsules all at once one morning. Approximately 36 hours after ingesting the three capsules, he experienced sudden visual loss in the left eye. He awoke the next morning and discovered blurred vision in the right eye and presented to our clinic.

He reported no pain or headache or any symptoms of systemic hypotension such as dizziness, cold sweats, or feeling faint. He admitted to habitually drinking approximately 500 mL of beer a day but did not smoke. He had been compliant with his antihypertensive medications. Toxicologic analysis revealed 32.22 mg sildenafil in each capsule of the Chinese health product.

He had no light perception in either eye. Both pupils were dilated and unreactive to light. Intraocular pressures were normal, and apart from the presence of mild cataracts and cup-to-disc ratios of 0.8 bilaterally, anterior and posterior segments were normal including the retinas. Both optic discs appeared pink.

Blood pressure throughout his subsequent 5-day stay in hospital averaged 130/80 mm Hg, ranging between 120/60 and 130/90 mm Hg. Complete blood count, erythrocyte sedimentation rate, and C-reactive protein, creatinine, VDRL, folate, and vitamin B12 levels were normal. Results of liver function testing were normal apart from decreased albumin (32 g/L; normal = 37–51 g/L) and elevated -glutamyltransferase (80 IU/L; normal = 11–63 IU/L). No mitochondrial DNA mutation at nucleotides 3460, 11778, or 14484 was found. Contrast-enhanced MRI scans with angiography of the brain and orbits was normal. Electroretinography was normal, and visual evoked potentials were absent.

After 6 weeks, visual acuity improved to count fingers in the right eye and hand movements in the left eye. Both optic discs were pale.

Nonarteritic anterior ischemic optic neuropathy has been reported to occur 30 minutes to 36 hours after ingestion of the phosphodiesterase-5 (PDE-5) inhibitor sildenafil (1,2), and a cause-and-effect relationship has been suggested.(3) We believe our patient suffered sequential nonarteritic posterior ischemic optic neuropathy (PION), which may occur in the setting of systemic vascular disease as well as systemic hypotension. Visual loss in our patient began approximately 36 hours after a relatively large dose (96.66 mg) of sildenafil. The short duration between the onset of visual loss in both eyes in the absence of other events that would have caused a drop in blood pressure, within a relatively short interval of taking the increased dose of sildenafil, suggests a possible role for that agent in the development of his visual loss. Diltiazem may have contributed by inhibiting cytochrome P450 3S4, the isoenzyme predominantly responsible for the metabolism of sildenafil (4) and prolonging the duration of action of sildenafil. To our knowledge, PION has not been reported in association with sildenafil. We postulate that a sildenafilinduced decrease in blood pressure (6), together with vasculopathic risk factors and antihypertensive therapy, contributed to its development.

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Stepwise Decline in Visual Field After Serial Sildenafil Use

Phosphodiesterase type-5 (PDE-5) inhibitors such as sildenafil, tadalafil, and vardenafil are widely prescribed in the treatment of erectile dysfunction. Previous reports (1–4) have described a temporal association of PDE-5 inhibitor use with nonarteritic anterior ischemic optic neuropathy (NAION). We report a patient who suffered three episodes of permanent visual field loss, each following closely after ingestion of 100 mg sildenafil.

A 63-year-old Caucasian man with erectile dysfunction had used 25 mg sildenafil episodically for 5 years without incident. He had essential hypertension treated with amlodipine. Two weeks after an uncomplicated prostatectomy for prostate cancer, he had attempted unsuccessfully to achieve erection using a single dose of 100 mg sildenafil. The next day, he noted "cloudiness" and a dark brown color in the inferior field of his left eye.

Ophthalmologic examination elsewhere 17 days after the 100 mg sildenafil dose disclosed a best-corrected visual acuity of 20/20 in both eyes. A left afferent pupillary defect was present. An inferior nerve fiber bundle visual field defect was present in the left eye. The visual field in the right eye was normal (Fig. 1). Ophthalmoscopic examination showed superior and nasal edema of the left optic disc with flame hemorrhages consistent with NAION. Results of the remainder of his ophthalmologic examination were normal, including nontender temporal arteries with intact pulsation and a normal sedimentation rate.

Over the next 14 days, he took two additional 100 mg doses of sildenafil. Within 24 hours of each dosing, he noted stepwise enlargement of the inferior visual field defect of the left eye. With the first decline, the defect expanded to cover the "lower 50%" of the left visual field. This defect remained stable until the next dosing when it expanded to involve his "line of sight." At that point, visual acuity in the left eye was documented at 20/40, but no formal visual field test was performed. He stopped using all PDE-5 inhibitors and was able to achieve erections using local injections of alprostadil. He reported no further visual field loss.

Six months after stopping the use of sildenafil, he requested a neuro-ophthalmologic evaluation. Best-corrected visual acuity was 20/20 in the right eye and 20/40 in the left eye. An afferent pupillary defect and dyschromatopsia were present in the left eye. Automated visual field analysis showed a full field in the right eye. In the left eye, there was an inferior nerve fiber bundle defect comparable to that seen in Figure 1 but with extension into the fixational region (Fig. 2). Ophthalmoscopic examination showed a normal right optic

disc (cup-to-disc ratio of 0.1) and a pale left optic disc. The remainder of the neuro-ophthalmologic examination was normal. Results of blood testing for the mitochondrial DNA mutations of Leber hereditary optic neuropathy were negative.

Previous reports have described NAION with symptom onset between 30 minutes and 36 hours after PDE-5 inhibitor ingestion (1–4). In the series of Pomeranz and Bhavsar (3), as in other published series (1,2,4), patients have had a high prevalence of established risk factors for NAION, including a "disc at risk" and arteriosclerotic risk factors (hypertension, hyperlipidemia, and coronary artery disease). Similar characteristics were noted among patients with NAION after tadalafil ingestion (5,6). Because of these confounders, many have questioned whether the PDE-5 inhibitor use and the subsequent NAION were unrelated.

Hence, rechallenge cases are important. Bollinger and Lee (5) described a case in which the patient experienced transient visual field loss within 2 hours of the first four doses of tadalafil. After the fifth dose, the patient developed unilateral NAION with persistent visual field loss. Pomeranz and Bhavsar (3) described a case of bilateral sequential NAION with continued use of sildenafil after the first occurrence of NAION.

Our patient is notable in having had a threestep decline in visual field after sequential use of sildenafil. We acknowledge that the visual field loss in NAION can expand spontaneously over several weeks after initial symptoms (7). Yet in our patient, each decline occurred within 24 hours of ingesting the agent and visual field analysis

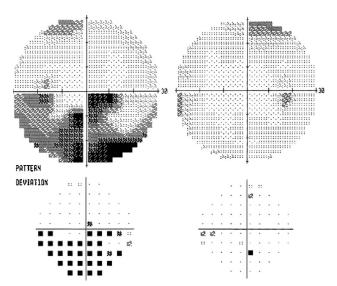


FIG. 1. Humphrey visual fields performed 17 days after 100 mg sildenafil use. They show an inferior nerve bundle defect in the left eye.

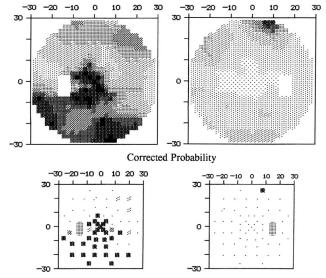


FIG. 2. Octopus visual fields performed 6 months after 100 mg sildenafil use. They show extension of the nerve fiber bundle defect of Figure 1 into the fixational area.

documented a worsening. Accordingly, it is tempting to consider that sildenafil played a precipitating role.

As with patients in other reports, our patient did have risk factors for spontaneous NAION (hyperopia and a small cup-to-disc ratio). And as for the other reported patients, he had used sildenafil for years without developing NAION. But the dose of sildenafil used just before stepwise visual field decline attributed to NAION events was four times larger than his usual dosage. Akash et al (1) have also reported the development of NAION shortly after excessive sildenafil dosage of 200 mg a few hours earlier. The patient had used sildenafil previously in a dose of 100 mg two to three times a week over a few months without side effects. It has been suggested that patients with a history of NAION avoid future PDE-5 inhibitor ingestion. This report supports such a recommendation.

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Intravitreal Triamcinolone for Nonarteritic Anterior Ischemic Optic Neuropathy

In a recent article in this journal, Kaderli et al (1) reported improved visual acuity outcomes and faster resolution of optic disc edema (ODE) in four eyes with nonarteritic anterior ischemic optic neuropathy (NAION) treated with intravitreal triamcinolone compared with six untreated eyes.

It is essential to place their findings in proper historical perspective. Nearly four decades ago, Foulds (2) stated that "A temporary ischaemia may lead to oedema of the nerve head which in turn further impedes capillary circulation leading to further anoxia so setting up a vicious circle." He (3) later stated that "Because increased capillary permeability appears to be an important factor in the development of a full picture of ischaemic optic neuropathy, we have recently been treating such patients with large doses of systemic steroids." He (3) reported his experience of systemic corticosteroid therapy in 24 patients with NAION showing significant visual acuity improvement compared with untreated patients. In 1974, I (4) reported visual acuity improvement in 75% of eight treated eyes with NAION compared with visual acuity improvement in 17% of six untreated eyes. By way of explanation, I (4) proposed that "Reduction of oedema by the steroid would relieve the pressure on the disc capillaries and restore some circulation in the vessels of the optic nerve head." We (5) also recently reported the effect of systemic corticosteroid therapy on ODE in a prospective study of 343 treated eyes with NAION and 380 untreated eyes with NAION; there was significantly (P = 0.0006) faster resolution of ODE in the treated group, independent of severity of initial visual field or visual acuity loss.

The study of Kaderli et al (1) has some notable flaws: 1. Their exclusion criterion was a visual acuity of better than 20/200. According to our study (6), that would exclude 75% of eyes with NAION one is likely to see. In our study (6), as well as in the Optic Nerve Sheath Decompression Study (7), only eyes with visual acuity of better than 20/70 were excluded from evaluation of visual acuity improvement or deterioration. Moreover, our natural history study (6) of visual outcome in NAION showed spontaneous visual acuity improvement in 41% (similar to that reported by the Optic Nerve Sheath Decompression Study (7)), and visual field improvement in 26% (6).

2. In their study (1), Although visual acuity improved in the treated eyes, no change in visual field defects was observed. We have found in studies on NAION and arteritic anterior ischemic optic neuropathy (AION) (6,8) that apparent visual acuity improvement without visual field improvement is due to eccentric fixation and does not represent a genuine improvement. Such patients evidently learn to read the visual acuity test chart better by looking around. This phenomenon applies particularly to eyes with altitudinal visual field defects or other defects that abut on fixation. In the series of Kaderli et al (1), all treated and untreated eyes had altitudinal visual field defects; eccentric fixation may therefore explain visual acuity improvement without visual field improvement.

3. The treated eyes were masked neither to the investigators nor to the patients, a study design that has the potential of introducing visual acuity testing bias. Moreover, the study is based on treatment of only four eyes.

In light of these limitations, one must accept their results with reservations.

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Reply:

We thank Dr. Hayreh for his comments on our article (1) and agree that the background and rationale of our study are more complete with the historical perspective he has contributed. Our replies to his main points are as follows:

1. Exclusion of eyes with visual acuity better than 20/200 in our study "would exclude 75% of the eyes with nonarteritic anterior ischemic optic neuropathy (NAION)" (2). Considering the possible complications of intravitreal triamcinolone and the lack of convincing evidence for efficacy of intravitreal triamcinolone in this disease process, we preferred to include only the most severely affected eyes.

2. The "apparent visual acuity improvement without visual field improvement is due to eccentric fixation and does not represent a genuine improvement," a phenomenon he has noted in cases of NAION and arteritic anterior ischemic optic neuropathy (AION) (2,3). We emphasize the unusually rapid reduction in optic disc edema in our triamcinolone-injected eyes. In their series of nine patients with radiation papillopathy who were receiving 4 mg intravitreal triamcinolone acetonide, Shields et al (4) reported that signs of optic neuropathy such as hyperemia and edema resolved within 1 month. The overall median (range) time to spontaneous resolution of optic disc edema from the onset of visual loss in NAION was 7.9 (5.8–11.4) weeks in the study of Hayreh and Zimmerman (5). These data suggest that intravitreal triamcinolone leads to faster recovery of optic disc edema than is seen in untreated NAION.

Whether intravitreal triamcinolone improves a reversible component of ischemic injury in NAION remains unclear. Visual field measurement may not be sensitive enough to detect a small amount of recovery of retinal ganglion cell axon function. More objective and sensitive methods for nerve fiber analysis such as Heidelberg retina tomography (6), optic coherence tomography (7), and scanning laser polarimetry (8) may help detect and compare the axonal loss in patients with treated and untreated NAION.

As we stated in our report (1), "The interpretation of our results is cautioned by the small sample size. Randomized studies with larger sample sizes are needed to show safety and efficacy."

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Animal Model for Nonarteritic Anterior Ischemic Optic Neuropathy

I want to comment on the issue of an animal model for nonarteritic anterior ischemic optic neuropathy (NAION) discussed by Kelman (1) in a recent editorial in this journal.

According to Bernstein et al (2), the animal model was produced by "argon laser light or frequency-doubling

yttrium-aluminum garnet laser (YAG)" application to the "intraretinal portion" of the optic nerve (the surface nerve fiber layer of the optic nerve head). To determine the validity of this animal model of NAION, one must consider the fundamental issues related to the blood supply of the optic nerve head (ONH) and the pathogenesis of NAION.

It is well established now that the ONH is supplied by two independent arterial sources. Its surface nerve fiber layer is supplied by the central retinal artery circulation and its deeper part by the posterior ciliary artery circulation (3,4).

NAION is due to vascular insufficiency in the deeper part of the ONH supplied by the posterior ciliary artery circulation only and not of the central retinal arterial circulation. Bernstein et al (2) produced thermal and tissue disruption lesions in the surface nerve fiber layer of the ONH (supplied by the central retinal artery circulation) and did not selectively produce hypoxia of the relevant deeper part of the ONH. Thus, the optic nerve damage produced in their animal model is somewhat akin to that produced by central retinal artery occlusion(5) and not by posterior ciliary artery vascular insufficiency.

Bernstein et al (2) claim that they produced "thrombosis" of the superficial layer of the ONH (supplied by the central retinal artery circulation). In fact, in addition to producing thrombosis, their method produced massive tissue damage in that layer as well. The argon laser produces generalized thermal injury at the site of application, and the YAG laser produces widespread generalized tissue damage both by heat and tissue disruption (like the explosion of a minibomb). Thus, in their model, there is generalized tissue damage of capillaries, axons, and glial tissue in the superficial nerve fiber layer of the ONH.

In NAION, by contrast, the ONH damage is caused by hypoxia of its deeper part. This is wholly different from the generalized thermal and tissue disruption injuries caused by argon and YAG lasers in the superficial nerve fiber layer. There is now ample evidence to support the concept of hypoxia causing the ONH damage in NAION (6,7). Hypoxic damage is most often produced by abnormal nocturnal arterial hypotension in persons with other risk factors (6,7). Vascular insufficiency in the ONH caused by abnormal nocturnal arterial hypotension is a transient phenomenon that does not always produce irreversible severe axonal damage. The proof is that in NAION there is a spontaneous visual improvement (8,9). In contrast, argon and YAG lasers produce thermal damage to the capillaries, axons, and other tissues in the ONH, and the YAG laser is highly disruptive, with irreversible, generalized, marked damage to all tissues in the superficial nerve fiber layer. Therefore, this animal model totally lacks the pathogenetic basis of NAION and

is unsuitable as an experimental model for studying this condition.

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Reply:

We want to reply to Dr. Hayreh's comments on the validity of our rat and mouse models for nonarteritic anterior ischemic optic neuropathy (NAION) (1,2). Dr. Hayreh's suggested explanations for the effects of the model are neither technically nor physiologically correct. Although we have great respect for Dr. Hayreh's previous work, he either misunderstands or is unfamiliar with the mechanisms of light activated-rose bengal photothrombosis and ignores the characteristics of the newer medical laser types and their effects in the power ranges used in our studies. In addition, he apparently has misinterpreted the site of the lesion induced in our model and bases his conclusions on his previous work. In fact, these conclusions can easily be refuted by a careful review of our published work (1-3) and of many other primary references (4-8), ranging from 1954 through the present day.

The rose bengal photoactivation model of NAION uses superoxide radical formation, not thermal energy. Rapidly degrading $(10^{-12} \text{ seconds})$ superoxide radical molecules damage the vascular endothelium, resulting in platelet-fibrin thrombosis of the vessels. Multiple reports (4-7) describe this process and its use in the retina as well as in other systems. The development of intravascular platelet-fibrin thrombi with this technique are well documented and are produced without using laser-generated coherent light. In producing our model, we used 514 nm (argon green) or 532 nm frequency-doubled yttrium-aluminum-garnet (fd-YAG) (green light) lasers because they effectively overlap and illuminate the capillaries supplying the anterior optic nerve without causing significant damage to surrounding tissue. Unlike the classical YAG laser (1,065 nm) that used destructive interference of two beams (what Dr. Hayreh describes as a "minibomb"), the fd-YAG laser is similar to an argon laser and has generally replaced the argon laser for the treatment of most ocular disorders.

We do not dispute the fact that high levels of laser power exposure coupled to large spot sizes can result in indiscriminate tissue necrosis and poorly discriminated deeper retinal damage (9), and we were mindful of the possibility of laser-induced thermal damage when we designed our studies. Indeed, in our reports, we include data showing that the low laser power we used (50 mW) and appropriate spot size sufficient to only illuminate the nerve do not produce significant thermal tissue damage. The rat anterior ischemic optic neuropathy (AION) model lesion was shown to be nonthermal by multiple methods: 1) a lack of vascular damage with laser exposure alone (sham treatment), which was determined by using India ink vascular mapping analysis (8) (1), revealing that only dye-coupled laser activation results in isolated optic nerve capillary loss, with continued patency of the larger central retinal vasculature (1); 2) no target neuron (retinal ganglion cell) loss with laser exposure alone (3); and 3) photo-induction-isolated retinal ganglion cell loss without disruption of deeper retinal cell layers. The above effects do not indicate any indiscriminate tissue damage induced by thermal necrosis (1).

Although photothrombosis of the optic nerve surface capillaries clearly occurs in our model, a more careful analysis of our data (2) also shows that there is a deeper focal effect in the retro-ocular optic nerve (the rodent does not have a lamina cribrosa), similar in depth to that clinically seen in the only early clinical case available (10). Dr. Hayreh's statement that "...NAION is due to vascular insufficiency in the deeper part of the ONH supplied by the posterior ciliary artery only" is also disputable. Dr. Hayreh provides no cited evidence for this statement, although there is much debate about the role of nocturnal hypotension in NAION. Unlike arteritic AION, for which Dr. Hayreh is due considerable credit, we are unaware of any cases of NAION that have been demonstrated to be due to vascular insufficiency in any specific bed.

We have never claimed that our rat AION model is identical to human NAION. Rather, we state that it has considerable similarities and that the responses of modeltreated animals are likely to be similar. The rat AION model is a tool that enables us to study individual events underlying the response of retinal ganglion cell neurons, as well as cellular events and responses of the vasculature and glial cells of the optic nerve. This tool can provide answers to questions about isolated optic nerve ischemia that have not and cannot be answered by other currently available methods. In short, the model that we have developed is and remains a valuable method for analysis of the effects of isolated optic nerve ischemia on the retina, optic nerve, and individual cell types. The model is likely to be useful for evaluation of neuroprotective strategies focused on treatment of isolated retinal ganglion cell (RGC) ischemic disease.

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I Am a Retinal Migraineur

Two recent publications in this journal (1,2) discussing retinal migraine have prompted me to report my personal history of multiple occurrences that I am calling "retinal migraine."

I am now a 71-year-old ophthalmologist with a 55year history of recurrent—often intense—unilateral headaches, lasting as long as 12 hours, frequently preceded by a short interval of enhanced sensitivity to light or sound and sometimes accompanied by nausea. The episodes are free of other visual disturbances.

I experienced my first homonymous scintillating scotoma without accompanying headache at age 25 as a small visual defect near central fixation. This developed into a fortification spectrum of silvery parallel zigzag lines that expanded peripherally, eventually disappearing in the nonpaired homonymous field after 15–20 minutes. Some of the lines had red and blue colored borders. Similar episodes have occurred up to the present time at intervals from one or two per week to one every few months. The scotomas have occurred in either hemifield but mostly on the right. They have uncommonly been associated with or followed by headache.

At age 56, I noted for the first time an unequivocally monocular absolute scotoma in the left inferior nasal field of the left eye near the point of fixation. It lasted 10 minutes, and I recorded it on an Amsler grid (Fig. 1A). Approximately 1 minute before the scotoma disappeared, the peripheral part of the scotoma began to contract, and the residual scotoma faded completely without any residual visual defect and without any accompanying systemic or neurologic manifestations. My pulse rate remained regular during the episode. Although I experienced some anxiety at the thought that this might represent an impending stroke, its short duration led to a self-diagnosis of retinal migraine. Nearly identical monocular events occurred in May 1993, December 1993, May 1999, May 2000, May 2003, November 2003, July 2003, December 2003, February 2005, December 2006, and February 2007. I have reproduced the scotomas of some of these events (Fig. 1B-D). In each event, the scotoma remained relatively stable for approximately 10 minutes and then receded over

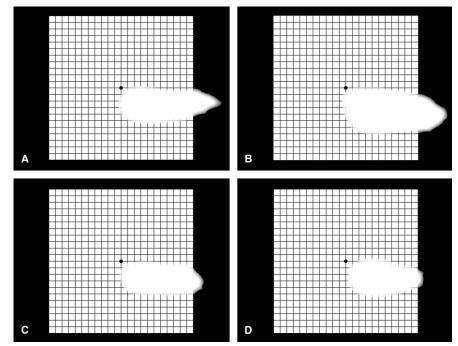


FIG. 1. Amsler grid self-recording of my left eye scotoma in 1992 (A), 1993 (B), 1999 (C), and 2007 (D).

1 minute. In February 2005, while I was driving an automobile, I experienced the only monocular event that involved my right eye.

At the beginning of the May 2003 event, I instilled tropicamide into my affected left eye. Within 6–7 minutes, I was examined by a retinal specialist working in an adjacent office, who found no evidence of retinal vasospasm, embolic phenomena, or other abnormalities. The scotoma persisted for approximately 2 minutes after the fundus examination.

The December 2003 monocular scotoma is thus far the only one with an accompanying headache (preceding the scotoma and lasting about 2 hours). The homonymous scintillating scotomas have continued but never during or even close to the time of the monocular events.

I have always been in good health, have had normal blood pressure and serum lipid levels, and have had no systemic or neurologic abnormalities requiring medications. None of the binocular or monocular visual events has had a temporal relationship to any of the commonly cited triggering events such as stress, fatigue, or ingestion of caffeine, alcohol, or spicy foods.

Winterkorn (2) has called "retinal migraine" an oxymoron because the retina does not appear to experience

spreading depression. Whatever you may wish to call these monocular visual events, they have been stereotypic, shortlived, isolated, life-long, benign, and present in a patient who has experienced migraine events with typical visual aura at other times. Retinal migraine has been an accepted term included in the 2004 International Headache Society classification (3). The absence of recognized vasospasm during one of my episodes does not preclude the possibility of vasospasm as an etiology, but it does beg for an alternative explanation.

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