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REVIEW ARTICLE

Ischemic optic neuropathies — where are we now?

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Abstract Ischemic optic neuropathy is of two types: anterior and posterior. Non-arteritic anterior ischemic optic neuropathy (NA-AION) is the most common type of ischemic optic neuropathy. There are three major misconceptions about NA-AION: (1) that its pathogenesis is not known, (2) that NA-AION and ischemic cerebral stroke are similar in nature, pathogenetically and in management, and (3) that there is no treatment. All these misconceptions are based on lack of in-depth knowledge of the subject. They are discussed in the light of our current scientific knowledge. The pathogenesis of NA-AION is known but is highly complex. NA-AION and ischemic cerebral stroke are very different clinical entities, pathogenetically and in management. Aspirin has no beneficial effect. Corticosteroid therapy during the initial stages can be beneficial. To reduce the risk of development of NA-AION in the other eye or of further visual loss in the same eye, it is essential to reduce as many risk factors as possible. Management of arteritic anterior ischemic optic neuropathy and of posterior ischemic optic neuropathy is discussed.

Keywords Anterior ischemic optic neuropathy · Giant cell arteritis · Ischemic optic neuropathies · Non-arteritic anterior ischemic optic neuropathy · Optic nerve · Posterior ischemic optic neuropathy

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Introduction

Ischemic optic neuropathy constitutes one of the major causes of blindness or seriously impaired vision among the middle-aged and elderly population, although no age is immune. In spite of that, its pathogenesis, clinical features, and management have been subjects of a good deal of controversy and confusion. This is primarily due to lack of an in-depth knowledge of the various aspects of the subject. Understanding and management of a disease is a three-step procedure.

1. *Most critical*: Good knowledge of the basic scientific facts of a disease is the fundamental requirement (after all, the basic sciences are the foundation of medicine).
2. That knowledge leads to a logical understanding of the pathogenesis of the disease.
3. That, then, finally results in its rational management.

To understand the basic scientific facts, pathogenesis, and clinical aspects of ischemic optic neuropathy, I have conducted the following research since 1955: (1) basic research on blood supply [1, 2] and structure [3] of the optic nerve, (2) experimentally produced anterior ischemic optic neuropathy (AION) in rhesus monkeys [4], and (3) clinical studies in more than 1,400 patients with various types of ischemic optic neuropathy. The objective of this review is to summarize our current understanding of the various types of ischemic optic neuropathy, mostly based on my multifaceted studies on its various aspects. A more detailed discussion of this is given elsewhere [5, 6]. Following is a very brief account.

Blood supply of the optic nerve

Since ischemic optic neuropathies are, by definition, ischemic disorders of the optic nerve, the first essential is to have an in-depth understanding about its blood supply (discussed at length elsewhere [1, 2, 5]). Based on blood supply, the

optic nerve can be divided into two parts: the anterior part (optic nerve head) and posterior part (Fig. 1).

The main source of blood supply to the optic nerve head is by the posterior ciliary artery circulation, except for the surface nerve fiber layer, which is supplied by the retinal circulation (Fig. 1 a). The blood supply in the optic nerve head is sectoral in nature, which is the reason why there is the sectoral involvement of the optic nerve head in ischemic disorders. A key fact is that the pattern of blood supply in the optic nerve head shows marked interindividual variation, and so, consequently, does the pattern of visual loss in its ischemic disorders.

The posterior part of the optic nerve is supplied by the pial vascular plexus, which is supplied by multiple pial branches originating from the peripapillary choroid, circle of Haller and Zinn, central retinal artery, ophthalmic artery, and other orbital arteries (Fig. 1 b). The anterior part of this region has an axial vascular system, which is present in 75 % of the optic nerves and is supplied by intraneural branches of the central retinal artery.

Factors which influence the blood flow in the optic nerve head are discussed at length elsewhere [7].

Types of ischemic optic neuropathy

Based on information on the blood supply of the optic nerve, I divided ischemic optic neuropathy into two types: [8, 9]

1. Anterior ischemic optic neuropathy (AION) involving the anterior part of the optic nerve (optic nerve head) is of two types:
   a. Arteritic AION: This is due to giant cell arteritis (GCA).
   b. Non-arteritic AION (NA-AION): This is due to other causes, and is much more common.
2. Posterior ischemic optic neuropathy (PION) involving the posterior part of the optic nerve, is of 3 types:
   a. Arteritic PION: This is due to GCA.

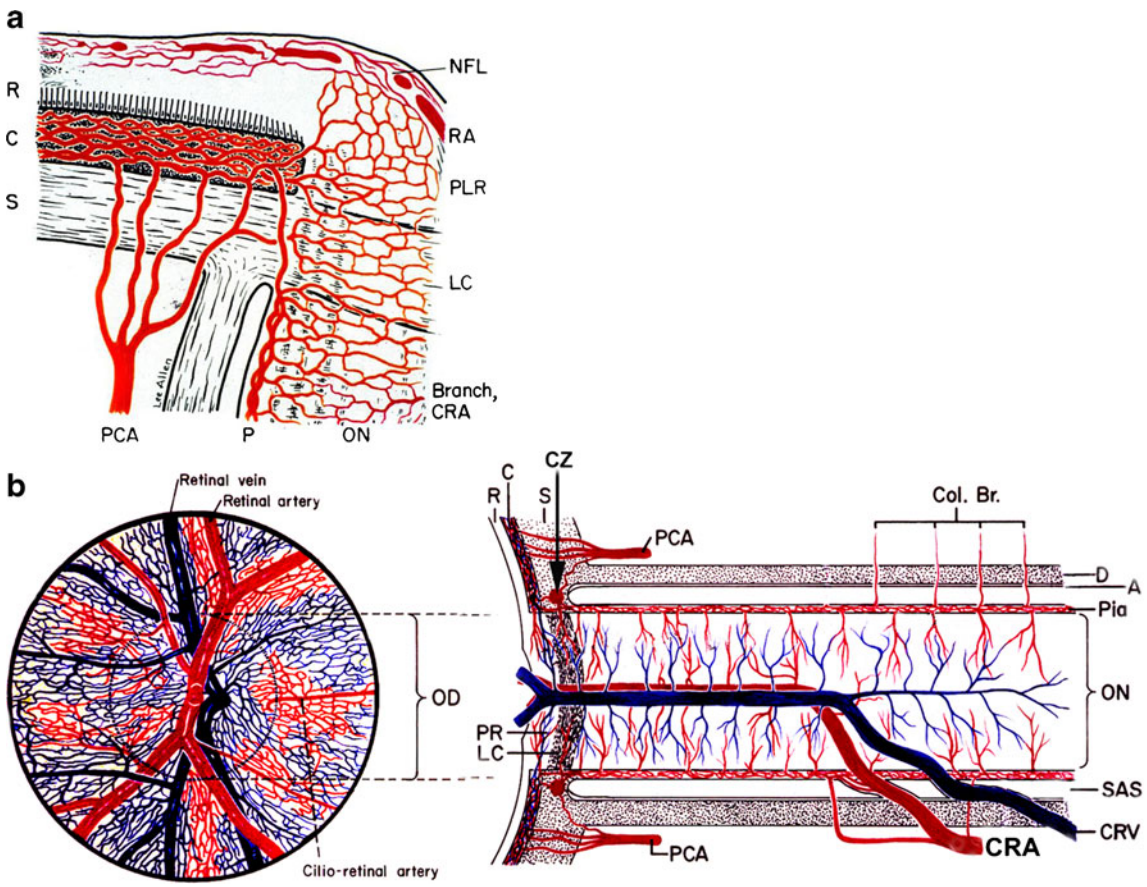

Fig. 1 **a** Schematic representation of blood supply of the optic nerve head [reproduced from Hayreh SS (1978) Structure and blood supply of the optic nerve. In: Heilmann K, Richardson KT (eds) Glaucoma: conceptions of a disease. Georg Theime, Stuttgart, pp. 78–96]. **b** Schematic representation of blood supply of the optic nerve [modified from Hayreh SS (1974) Anatomy and physiology of the optic nerve head. Trans Am Acad Ophthalmol Otolaryngol 78:OP240-OP254]. *A* = arachnoid; *C* = choroid; *CRA* = central retinal artery; *Col. Br.* = collateral branches; *CRV* = central retinal vein; *D* = dura; *LC* = lamina cribrosa; *NFL* = nerve fiber layer; *ON* = optic nerve; *P* = pia mater; *PCA* = posterior ciliary artery; *PR, PLR* = prelaminar region; *R* = retina; *RA* = retinal artery; *S* = sclera; *SAS* = subarachnoid space

b. Non-arteritic PION: This is due to other causes, and is the most common type.
c. Surgical PION: This is associated with various extraocular surgical procedures. This has also been called postoperative or perioperative PION. I have used the term "surgical PION" because it is more inclusive.

Relative frequency of various types of ischemic optic neuropathy

Previously there was little information on this subject. I analyzed this in all patients with ischemic optic neuropathies seen in my clinic from 1973 to 2008. There were about 1,400 patients. I analyzed the relative frequency of the various types of ischemic optic neuropathy among this cohort [5]. The relative frequencies of AION and PION were 96 % and 4 % respectively. Since PION is a diagnosis of exclusion [9], however, it may sometimes have been missed, so that the frequency I found may be a slight underestimate..

Anterior ischemic optic neuropathy The total number of patients seen in my clinic with this condition was about 1,350. Of those, about 90 % had non-arteritic anterior ischemic optic neuropathy (NA-AION) and 10 % arteritic anterior ischemic optic neuropathy.

Posterior ischemic optic neuropathy There were about 50 patients. Of those, about 66 % had non-arteritic PION, 26 % arteritic PION, and 7 % surgical PION.

Anterior ischemic optic neuropathy (AION)

As discussed above, AION is of two types: NA-AION and arteritic AION.

Non-arteritic anterior ischemic optic neuropathy (NA-AION)

Misconceptions about NA-AION

There are several fundamental misconceptions about NA-AION, which have resulted in controversies and confusion on various aspects of NA-AION [5, 6]. Following are the three major misconceptions relevant to the present discussion.

I. That its pathogenesis is not known.
II. That NA-AION and ischemic cerebral stroke are similar in nature, pathogenetically and in management.
III. That there is no known treatment.

Unfortunately, all these misconceptions are based on lack of in-depth current knowledge of the subject. I have discussed them at length elsewhere [5, 6]. Following is a brief discussion, in the light of our present knowledge of the subject.

That its pathogenesis is not known

The pathogenesis of NA-AION is discussed at length elsewhere [5, 6, 10]. Briefly, NA-AION is due to acute ischemia of the optic nerve head, and it is a *multifactorial disease*. This means many risk factors play roles in its development, and *there is no one culprit which causes it*. Various risk factors, which play a role in its development, can be divided into two main categories: (i) predisposing risk factors and (ii) precipitating risk factor(s) [11].

Predisposing risk factors These may be systemic risk factors or local risk factors in the optic nerve head.

Systemic risk factors	These include diabetes mellitus [11, 12], arterial hypotension [13, 14], arterial hypertension [11], blood loss [15], atherosclerosis [11], sleep apnea [10, 16], cardiovascular disorders [11], migraine [10], arteriosclerosis, type A personality [10], and other risk factors as yet unknown.
Local risk factors in the optic nerve head [7]	These include poor optic nerve head blood supply, posterior ciliary artery disease, location of posterior ciliary artery watershed zones in relation to the optic nerve head, vasospasm, defective autoregulation of optic nerve head blood flow, raised intraocular pressure, chronic optic disc edema due to any cause, optic disc drusen, and other unknown risk factors.

Time of onset of NA-AION This provides important information about the pathogenesis. My study [17] showed that of 925 episodes of NA-AION, 73 % of patients gave a history, when specifically asked, of discovering their visual loss on awakening from sleep in the morning or from a nap, or at the first opportunity in the day to use their vision critically. The incidence may actually be much higher than 73 % because other patients, who first became aware of their visual loss later in the day, could not be certain when it had first occurred, nor could they rule out the possibility that it had been there since awakening [17].

I did 24-h ambulatory blood pressure monitoring studies, recording blood pressure every 10 min during waking hours and every 20 min during sleeping hours in about 700 patients [13, 14]. Those revealed that, while blood pressure may be perfectly normal during the day, it drops during sleep — much more in some persons than in others. Figure 2 shows the 24-h ambulatory blood pressure monitoring graph in a patient who developed NA-AION, first in one eye and later on in the second. It shows that during her waking hours, the blood pressure was within normal limits but that soon after going to sleep, systolic blood pressure fell from 140 mmHg to 90 mmHg and diastolic from about 80 mmHg to about 50 mmHg. Her blood pressure was low throughout her sleeping hours. This is called *nocturnal arterial hypotension*. My 24-h ambulatory blood pressure monitoring studies showed that daytime blood pressure is almost invariably normal, but that is not at all a guide to the blood pressure during sleep, as can be seen in Figure 2. Unfortunately, most of the information on blood pressure is based on daytime recording.

Nocturnal arterial hypotension A certain amount of fall of blood pressure during sleep is physiological, but it can be aggravated by medication, most commonly by aggressive antihypertensive therapy with beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and other hypotensive drugs, especially when those are taken at bedtime or in the evening [13, 17–19]. Figure 3 demonstrates that very well. This patient was taking Verapamil (a calcium channel blocker) 3 times a day (160 mg morning and bedtime, and 80 mg noon) for migraine; with that, the systolic blood pressure dropped from about 135 mmHg during waking hours to as low as about 80 mmHg during sleep, and diastolic blood pressure dropped from about 70 mmHg during the day to as low as about 35 mmHg during sleep. On stopping the bedtime dose, there was a marked decrease in the fall of blood pressure during sleep. Nocturnal arterial hypotension can occasionally develop without any such medication, as occurred in the case shown in Fig. 2; this is most probably due to defective cardiovascular autoregulation.

It is interesting to find that before 1960, i.e., before the advent of beta-blockers and other potent modern blood pressure lowering drugs, NA-AION was an uncommon disease. Now, as potent antihypertensive drugs are frequently prescribed by physicians, NA-AION has become a common disease, indicating the likelihood that they may be playing a role in its increased incidence.

In persons with predisposing risk factors, precipitating factor(s) then act as the final insult and produce NA-AION. In the vast majority, visual loss develops during sleep [17]. This indicates that nocturnal arterial hypotension is the most common precipitating risk factor. In view of all this information, we can say confidently that *NA-AION is a hypotensive disorder*. It is due to transient non-perfusion or hypoperfusion of the blood vessels in the optic nerve head during sleep, and *not* due to occlusion of the PCAs as often stated. Fluorescein fundus angiography provides the best proof of that, as shown by Fig. 4.

The argument put forward by those who doubt the role of nocturnal arterial hypotension in the pathogenesis of NA-AION, and the hypotensive nature of NA-AION, is that in the prospective NA-AION Multicenter Decompression Trial

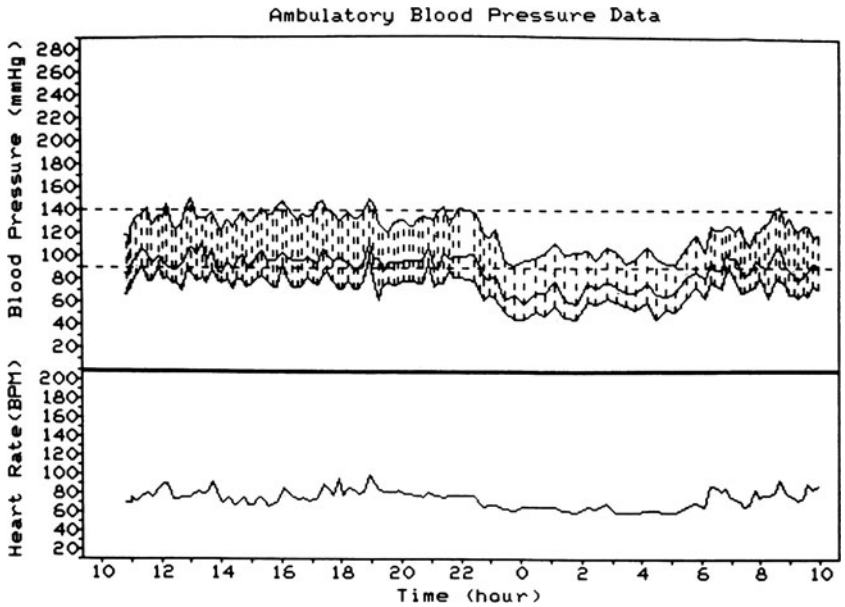

Fig. 2 24-h ambulatory blood pressure recording in a patient who developed NA-AION first in one eye and later on in the second eye. This patient was not on any medication, and yet showed marked nocturnal arterial hypotension, with a drop of systolic blood pressure from 140 mmHg during the day to as low as 90 mmHg during sleep, and diastolic blood pressure from about 80 mmHg during the day to about 50 mmHg during sleep. Reproduced from Hayreh et al [14]

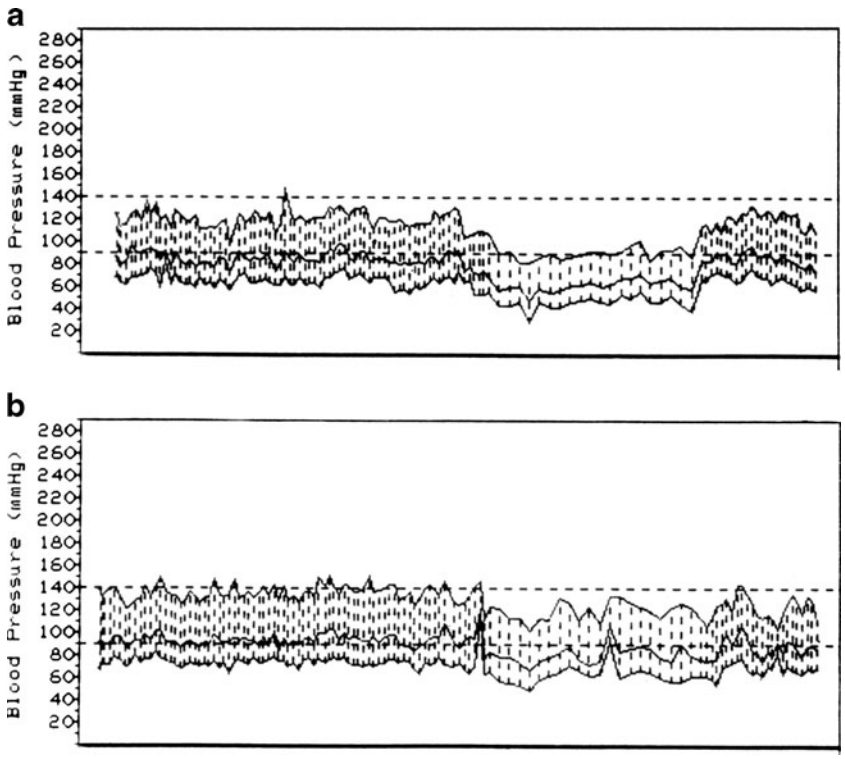

Fig. 3 24-h ambulatory blood pressure recording in a patient taking Verapamil (a calcium channel blocker). **a** When on 160 mg morning and bedtime and 80 mg at noon, during sleep systolic blood pressure dropped from 135 mg/Hg to 80 mg/Hg and diastolic from 70 mm/Hg to about 35 mmHg. **b** On stopping the bedtime dose, nocturnal hypotension improved markedly. Reproduced from Hayreh [16]

Study [20] only 42 % of the 418 patients reported the onset of visual loss within 2 h of awakening. This is in sharp contrast to the findings of my prospective study [17] where, as mentioned above, 73 % of patients gave a definite history, *when specifically asked*, of discovering their visual loss on awakening in the morning or from a nap, or at the first opportunity in the day to use their vision critically (the rest were not sure of the time). The findings of these two prospective studies do conflict, and that has resulted in controversy on the important concept of the hypotensive nature of NA-AION. However, study design determines the quality of the data. The accuracy of this historical information can be largely influenced by: (i) the expertise of the person asking the questions, and (ii) the manner in which the patient is asked about when their visual loss was first noticed, and the circumstances of how they became aware of it. In my study [17], I

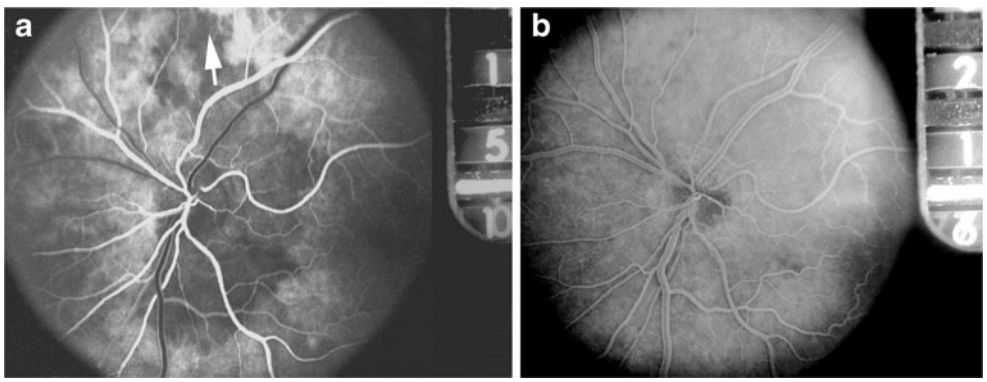

Fig. 4 Fluorescein angiograms of left eye 12 days after development of NA-AION. **a** Fifteen seconds after the injection of fluorescein shows no filling of the temporal, superior, and inferior peripapillary choroid (main source of blood supply to the ONH), superior choroidal watershed zone (*arrow*), and the optic disc, with normal filling of both the medial and lateral posterior ciliary arteries. **b** Six seconds after **a** shows complete filling of the peripapillary choroid, the watershed zone and upper part of the disc. Reproduced from Hayreh [6]

personally collected the historical information from each patient with NA-AION, and learned that the accuracy of a patient's recall depends upon non-suggestive, unbiased, yet thorough questioning. Often the patient needs to be made aware of the importance of their recollection of their discovery of visual loss. In the NA-AION Multicenter Decompression study [20], historical information was collected by many individuals (of different levels of expertise) at different study sites, by necessity, and may not be as rigorous as in my study. It is more challenging in such a heterogeneous study to collect such historical information methodically, uniformly, and reliably enough to reach an accurate estimate of the true proportion of patients whose visual loss occurred soon after awakening. Estimates of visual loss on awakening in patients with NA-AION may be largely underestimated if based primarily on what the patients volunteer rather than the answers to specific, directed questioning. Moreover, the criterion used in that study of onset of visual loss occurring within 2 h of awakening was not valid, because the answer depends upon when the patients first tried to use their vision critically during the day. I think that explains the important discrepancy between my study [17] and that of the NA-AION Multicenter Decompression Trial Study [20]. That should help us to understand the controversy with regard to the hypotensive nature of NA-AION.

In conclusion, *the pathogenesis of NA-AION is known, but it is highly complex*. It is multifactorial in nature. Whole hosts of systemic and local risk factors, acting in different combinations, predispose an optic nerve head to develop NA-AION. There are serious confounding factors in determining risk factors for NA-AION; those are discussed in detail elsewhere [21]. One of the arguments often put forward by those who believe the pathogenesis of NA-AION is not yet known is that some patients with NA-AION seem perfectly healthy, with no known risk factors. The inability to pinpoint a risk factor may be due to several reasons (discussed elsewhere [21]). *Thus, the axiom should be that just because one does not find any evident risk factor, that does not necessarily mean that that person actually has no risk factor.*

That NA-AION and ischemic cerebral stroke are similar in nature pathogenetically and in management

As discussed above, NA-AION is a hypotensive disorder in the majority of cases and only very rarely a thromboembolic disorder. Ischemic cerebral stroke, on the other hand, is usually a thromboembolic disorder and occasionally hypotensive. Thus, it is a fundamental mistake to equate the pathogeneses of the two conditions, and this mistake has implications in the management of NA-AION. I have discussed this subject at length elsewhere [16].

That there is no known treatment

This is the most important subject in the management of NA-AION, and requires discussion at length. In any disease, to place a treatment in proper perspective, the first essential is to know its natural history, i.e., what happens without any treatment. I investigated prospectively the natural history of visual outcome in 386 eyes with NA-AION, first seen ≤2 weeks after onset [22]. This investigation showed that in eyes with initial visual acuity of 20/70 or worse, visual acuity improved spontaneously in 41 % at 6 months after the initial visit, and in none after that. In eyes with moderate to severe visual field defects, there was spontaneous improvement in 26 % at 6 months after the initial visit [22]. None showed any change after that. Similarly, in the Ischemic Optic Neuropathy Decompression Trial study [20], visual acuity improved in 43 % of untreated eyes with visual acuity of 20/70 or worse, seen within 2 weeks after the onset of NA-AION.

Various treatments that have been advocated in NA-AION are discussed at length elsewhere [5]. Here I shall discuss only two of them.

Aspirin in NA-AION

Ophthalmologists and neurologists routinely tend to prescribe aspirin to NA-AION patients in the belief that, like stroke, it is a thromboembolic disorder and aspirin helps thromboembolic disorders. However, two large studies, one in 431 patients [23] and another one in 173 patients [24], have shown that aspirin has no long-term benefit of reducing the risk of NA-AION. This is because NA-AION is *not* a thromboembolic disorder but a hypotensive disorder, and aspirin has no effect on blood pressure.

Systemic corticosteroid therapy in NA-AION

The beneficial effect of high-dose systemic corticosteroids during the acute phase, when there is optic disc edema, has become highly controversial. Therefore, it is important to discuss it at length to clarify the current confusion and controversy.

A small study by Foulds [25] at the University of Glasgow, Scotland, in 1969, and my own preliminary study [26] at the University of Edinburgh, Scotland, in 1972, indicated that systemic corticosteroids in NA-AION may improve visual acuity. Based on that information, in 1973 I planned a large, multicenter randomized clinical trial to investigate systematically in a large cohort of NA-AION patients whether systemic corticosteroids improved visual outcome or not. Unfortunately, that clinical trial was not funded by the National Institute of Health (the main research funding agency in the United States), because of a firm belief among neuro-

ophthalmologists (equating ischemic stroke and NA-AION as pathogenetically similar in nature) that corticosteroid therapy has no role in NA-AION. Since no alternative treatment existed, I felt that it was crucial to find out whether corticosteroid therapy was actually beneficial, ineffective, or conceivably harmful in NA-AION. Because no funds were available, instead of the "conventional randomized study", I decided on a *"patient choice"* study — the next best choice. Every NA-AION patient seen in my clinic was given a free and informed "patient choice". The decision was left entirely up to the patient, to opt for corticosteroid therapy or no treatment, in consultation with their physicians or other sources. Most importantly, we had no input at all into their choice. I specifically told all patients that I really did not know whether the treatment was beneficial, ineffective, or even harmful.

I collected the data for 28 years, completely masked about visual outcomes, numbers, and other aspects of patients in the study. The study finally included 613 consecutive NA-AION patients (696 eyes) seen in my clinic. The results are discussed at length elsewhere [27].

Treatment protocol

Initially 80 mg prednisone daily was given for 2 weeks, then tapered down to 70 mg for 5 days, 60 mg for 5 days, after that cut down by 5 mg every 5 days, to nothing [27].

Data analysis of the study [27]

This revealed the following four surprises.

1. Of the 613 patients with NA-AION, 51 % voluntarily opted for systemic corticosteroid therapy and 49 % opted for no treatment. This was a total surprise: after collecting data for 28 years, it turned out that equal numbers of patients opted for and against treatment.
2. Equally surprising was that rigorous statistical testing [27] found *no* statistically significant difference between the two groups in visual acuity and visual fields. Also, there was no significant difference in systemic diseases in the two groups, except that patients who opted for treatment were slightly younger (59.2 vs 62.0 years) and had a lower prevalence of arterial hypertension (34 % vs 43 %). To determine if those two factors influenced the visual outcome, they were *accounted for* in the statistical analysis by including them as covariates in the logistic regression model; that showed that they made *no* difference in visual outcome (age $p=0.8$; hypertension $p=0.6$), so that in fact there was no significant difference in systemic diseases between the two groups in the study to influence the visual outcome.

   The most crucial requirements in any "randomized clinical trial" are that the treated and untreated groups must be comparable in demographic and clinical characteristics. As is evident from the above, my "patient choice" study definitely fulfilled those crucial criteria of a "randomized clinical trial".
3. Of the NA-AION eyes with initial visual acuity of 20/70 or worse, seen within 2 weeks of onset, visual acuity improved in 70 % of the treated group compared to 41 % in the untreated group (odds ratio of improvement: 3.39; $p=0.001$). Of the NA-AION eyes with moderate to severe initial visual field defects, seen within 2 weeks of onset, visual field improved in 40 % in the treated group compared to 25 % in the untreated group (odds ratio: 2.06; $p=0.005$).
4. In both treated and untreated groups, visual acuity and visual fields improved for up to 6 months after onset of NA-AION, but no more after that [22, 27].

Conclusion of the study [27]

Thus, the study showed that treating NA-AION eyes within the first 2 weeks after onset with high-dose systemic corticosteroids results in a significantly higher probability of improvement in visual acuity ($p=0.001$) and visual fields ($p=0.005$), compared to an untreated group. Both visual acuity and visual fields improved for up to 6 months after onset of NA-AION, and no more after that.

Objections by neuro-ophthalmologists to my study

Most neuro-ophthalmologists have been unwilling to accept the findings of my study [27]. They have raised the following objections:

First objection Most importantly, that there is no scientific rationale for the use of corticosteroid therapy in NA-AION.

This is discussed in detail elsewhere [5, 27]. The following two factors are the rationale for the use of corticosteroid therapy in NA-AION.

1. NA-AION is due to ischemia of the optic nerve head. Initially there is always optic disc edema, due to two factors;
   (i). *Axonal ischemia* → Axoplasmic flow stasis → Swollen axons → Disc swelling.
   (ii). *Capillary leakage in optic nerve head*: this is always shown by optic disc staining on fluorescein fundus angiography (Fig. 5). It is caused by: (a) ischemic insult to capillaries, and (b) venous stasis from axonal swelling [28].

Fig. 5 Fluorescein fundus angiogram showing late fluorescein staining of the optic disc in NA-AION

It is well-known that corticosteroids reduce capillary permeability, and that reduces fluid leakage and edema. For example, it is well-established that in macular edema, intravitreal corticosteroid therapy reduces fluid leakage and consequently reduces macular edema. A comparison of the time it took for resolution of optic disc edema in NA-AION patients treated with corticosteroid therapy versus untreated patients showed a faster resolution of optic disc edema in the treated group (p= 0.0006) [29].

In view of all these facts, the scientific rationale for visual improvement with corticosteroid therapy in NA-AION is this: faster resolution of optic disc edema with corticosteroid therapy [29] → progressive decrease of compression of the capillaries in the optic nerve head → restoration of better blood flow in the capillaries → improved circulation in the optic nerve head → improved function of the surviving but not functioning hypoxic axons → Improved visual outcome.

2. Bernstein and colleagues showed in experimental NA-AION that "cellular inflammation plays a major early role following white-matter (optic nerve) infarct" [30] and that "inflammation is a prominent early histological feature" [31]. They also showed, in one human NA-AION specimen, evidence of acute inflammation in the region of the infarct as well as in the surrounding regions [31]. Based on their studies, they concluded that "selective inflammatory modulation also may be relevant in the treatment of human NAION treatment" [31]. It is well-established that corticosteroid therapy is the treatment of choice in inflammatory disorders. Thus, the presence of inflammatory reaction in acute NA-AION is another rationale for the use of corticosteroid therapy and its beneficial effect.

Therefore, the faster resolution of optic disc edema [29] and presence of inflammatory reaction [30, 31] in NA-AION constitute a rationale for the beneficial effect of corticosteroid therapy in NA-AION.

Second objection That there was no "conventional randomization" in my study.

This raises the issue: what are the critical criteria for "conventional randomization"? As discussed above, in "conventional randomization", it is essential to have comparable treated and untreated groups at baseline in demographic and clinical characteristics. In my study [27], as discussed above, there was no significant difference between the treated and untreated groups in the baseline demographic and clinical characteristics. Thus, my "patient randomization" study *did* fulfill all the basic critical criteria for "conventional randomization". When all these facts are put together, one can conclude that the information provided by my "patient randomization" in my study [27] was as scientifically valid as that in "conventional randomization", about the role of corticosteroid therapy in NA-AION.

Third objection The study data were not collected in a masked fashion.

From the start of the study, I was aware that this would be an objection. In my paper [27], I specifically discussed at length what steps were taken to ensure masking, both in data collection and during data analysis.

The Ischemic Optic Neuropathy Decompression Trial study [20] was a "randomized" and "masked" study. In that study, in patients with visual acuity of 20/70 or worse, seen within 2 weeks after the onset of NA-AION, visual acuity improved in 43 % of untreated eyes. In my study [27], in an exactly identical group of NA-AION patients (i.e., those with visual acuity of 20/70 or worse and seen within 2 weeks after the onset), visual acuity improved in 41 %. In both studies, the visual acuity kept improving only for the first 6 months. Thus, my study [27] had findings absolutely identical to that of the Ischemic Optic Neuropathy Decompression Trial study [20]. This is the most convincing evidence that the visual acuity data in my study were unbiased.

Fourth objection That "Oral corticosteroids in the setting of acute cerebral stroke are contraindicated" [32].

This implies that the pathogenesis and management of acute ischemic cerebral stroke and NA-AION are similar. As discussed above and elsewhere [16], pathogenetically the two conditions are totally different clinical entities. *Ischemic cerebral stroke is usually a thromboembolic disorder*, involving a large mass of tissue in the cerebrum. In sharp contrast to that,

NA-AION is usually a hypotensive disorder, with comparatively mild ischemia due to only transient non-perfusion or hypoperfusion of the blood vessels in the ONH during sleep, and involving a minute amount of tissue in the ONH. *Therefore, to equate the two conditions is a fundamental mistake*.

In spite of my clarifying all the objections, some neuro-ophthalmologists still believe that corticosteroid therapy has no beneficial effect in NA-AION. Scientific knowledge is constantly evolving; as our knowledge advances, our concept of a disease and its management must change too. Therefore, one has to evaluate findings in the light of current knowledge and scientific evidence, rather than outmoded conventional thinking. Over my 57 years of research, based on my findings, I have often challenged dogmas and conventional wisdom. Whenever conventional wisdom is challenged, even if new scientific information shows that it is no longer valid, the initial reaction is almost always skepticism or even ridicule. I have faced that problem many times during my research over the years; fortunately, the findings of my studies have stood the test of time.

Who, when and how to treat NA-AION patients with corticosteroid therapy?

The sooner the treatment is started, the better are the chances of visual improvement. That may be because the shorter the duration of axonal ischemia, the fewer axons are likely to be damaged permanently.

Secret of systemic corticosteroid therapy success

Among many physicians there seems to be resistance, almost amounting to a phobia of corticosteroid therapy, particularly high-dose corticosteroid therapy, especially in the elderly. (On a personal note, I myself developed GCA several years ago and have been on corticosteroid therapy since then — and I am 85 years old.) One of my interests during the past 45 years has been rheumatological diseases of the eye, including scleritis, uveitis, orbital myositis, ocular vasculitis, and GCA. I have treated several thousand patients of all ages with high-dose systemic corticosteroid therapy required to treat these conditions. I have found that the most effective method to is to "hit hard at the beginning and then taper down". The major flaw in the way corticosteroid therapy has been given for NA-AION in some studies is "too small a dose, for too short a period". This timidity has led to the prevailing misconception that corticosteroid therapy is ineffective in NA-AION.

Reduction of risk factors

Almost invariably, patients are told that "there is no treatment for NA-AION, and nothing more can be done to help". *That advice is wrong*. Most importantly, as discussed above, NA-AION is a multifactorial disease. To reduce the risk of development of NA-AION in the other eye or of further visual loss in the same eye, it is essential to reduce as many risk factors as possible. All patients require thorough evaluation for risk factors. As discussed above, inability to find a risk factor may be due to several reasons discussed elsewhere [21]. *Thus, the axiom should be that if one does not find any evident risk factor, that does not necessarily mean that person actually has no risk factor.*

As discussed above, nocturnal arterial hypotension is an important risk factor for NA-AION. Hence, management of nocturnal arterial hypotension is an important step in management and reducing the risk of NA-AION. The most common cause of nocturnal arterial hypotension is over-medication with antihypertensive drugs, or taking these drugs at bedtime (Fig. 3). Therefore, I strongly recommend that when a patient is at risk of developing NA-AION or has a history of NA-AION in one eye, the treating physician should be made aware of the potential risks of intensive arterial hypotensive therapy - particularly to avoid it in the evening or bedtime.

Two frequently asked questions by patients with NA-AION

1. *What is the risk of second eye involvement by NA-AION*? The cumulative probability of the fellow eye developing NA-AION has varied among different reported studies: 25 % within 3 years in 438 patients [33], 17 % in 5 years in 431 patients [23], and 15 % over 5 years in 326 patients [24]; however, different criteria were used to determine the probability, which may explain the differences.
2. *What is the risk of more than one episode of developing NA-AION in the same eye*? In my study of 829 eyes with NA-AION, ipsilateral recurrence of NA-AION was 6.4 % [34]. The study showed that overall, patients with recurrence of NA-AION had a significantly lower mean nighttime minimum diastolic blood pressure (p=0.003) and greater mean percentage drop during sleep in diastolic blood pressure (p=0.011) than those with no recurrence of NA-AION. Thus, presence of nocturnal arterial hypotension was the only significant factor in these patients.

In sequential bilateral NA-AION, is the visual outcome in the two eyes similar or not?

In patients with sequential bilateral NA-AION, from a prognostic point of view, it would be useful to know whether the visual outcome in the two eyes is likely to be similar or not. In the literature there is conflicting information [35]. I investigated this in 174 consecutive sequential bilateral NA-AION patients [35]. That study showed that in bilateral sequential NA-AION patients, there are large differences between the visual acuity and visual field findings of paired eyes at initial and final visit. Interestingly, both initial visual acuity and visual field defects were significantly better in the

second eye than in the first ($p<0.0001$). Therefore, from a prognostic point of view, it is not possible to predict the second eye's visual acuity and visual field grade based solely on the first eye.

NA-AION conclusions

From the above discussion, one can draw the following conclusions:

1. The pathogenesis of NA-AION is known but is highly complex.
2. High-dose corticosteroid therapy during the initial stages has rationale and can be beneficial.
3. Aspirin has no beneficial effect.
4. Risk factors must be eliminated to reduce the risk of further visual loss.
5. It is not adequate to predict the second eye's visual acuity and visual field grade based solely on the first eye.

Management of arteritic AION

Arteritic AION is due to GCA, which is an *ocular emergency; it requires early diagnosis and management to prevent visual loss*. These issues are discussed at length elsewhere [5, 36]. It is well-established that high-dose systemic corticosteroid therapy is the treatment of choice. Corticosteroid therapy in GCA is discussed at length elsewhere [5, 36].

When a patient aged 50 years or older is seen with AION, the first essential is to determine whether it is due to GCA or not, by immediately doing erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) estimations; other findings suggesting GCA are the presence of systemic symptoms of GCA and arteritic AION. Conventionally, diagnosis of GCA is based on systemic symptoms of GCA and elevated ESR. However, both these parameters may be misleading in some patients. It is well-established that normal ESR does not always rule out GCA [36, 37]. For example, I have seen temporal artery biopsy-confirmed GCA patients with Westergren ESR as low as 4 or 5 mm/h [36, 37]. Similarly, there is the clinical entity of *occult GCA* [37], in which patients have no systemic symptoms of GCA at all; in my study [38], 21 % of patients who lost vision due to GCA had incipient GCA. Thus, *the presence of normal ESR and absence of systemic symptoms does not rule out GCA; elevated CRP level is a far more reliable sign*. Also, at presentation, differentiation of arteritic AION from NA-AION is critical; the various criteria which can help to do that are discussed elsewhere [5, 36, 39]. Fluorescein fundus angiography provides useful information here, because in arteritic AION, during the initial stage, there is almost invariably absence of filling of the choroid in the distribution of the posterior ciliary artery occluded by GCA.

My studies on GCA have shown that *the only logical way to manage corticosteroid therapy in GCA to prevent visual loss is to be guided by estimation of ESR and CRP levels, and not by systemic symptoms*, as discussed elsewhere [5, 36]. GCA patients almost always require lifelong corticosteroid therapy to prevent visual loss. *Importantly, visual loss in GCA is preventable with adequate corticosteroid therapy.*

There has been controversy about whether high-dose intravenous or just oral corticosteroid therapy is required in treatment of acute visual loss in GCA. This controversy is discussed at length elsewhere [40]. My recommendation in these cases is as follows: For all patients, with or without vision loss, I initially begin with a dose of at least 80 mg oral prednisone daily, except in the following three situations:

(1) A history of amaurosis fugax but no visual loss; amaurosis fugax is an ominous sign of impending visual loss.
(2) Complete or marked loss of vision (judged by both visual acuity and visual field— particularly the latter) in one eye.
(3) Early signs of involvement of the second eye.

In these conditions, it is essential to act urgently to achieve high levels of corticosteroid concentration in the circulation as soon as possible. Oral corticosteroid therapy takes some time to achieve high levels in the circulation. Therefore, I initially give these patients one megadose of intravenous corticosteroid (as outpatients), immediately followed by the oral corticosteroid regimen, starting with 80 mg prednisone daily.

Posterior ischemic optic neuropathy (PION)

I first described this as a distinct clinical entity in 1981 [9]. Since then, innumerable reports have been published, but all of them except two are anecdotal case reports, based on 1–2 patients only. The exceptions are: (1) by Isayama et al. [41] in 14 PION patients, and (2) by Sadda et al. [42] in 72 PION patients.

I have discussed the literature, classification, pathogenesis, clinical features, and management of PION at length elsewhere, based on a study of 53 consecutive eyes with PION seen in my clinic [5, 43]. As discussed above, PION is of three types: arteritic PION due to GCA, non-arteritic PION, and surgical PION.

Clinically, initially there is a sudden painless visual loss in one or both eyes, with defective visual acuity and visual fields, but normal optic disc, fundus, and rest of the ophthalmic evaluation. In view of that, I stress that PION is a diagnosis of exclusion [9]. In surgical PION, visual loss is

usually discovered on waking from the surgical procedure, and it tends to cause bilateral, massive visual loss or even complete blindness, which is usually permanent.

Management of PION

Arteritic PION

Since this is due to GCA, high-dose systemic corticosteroid therapy is a well-established treatment to prevent any further visual loss. Corticosteroid therapy in GCA is discussed at length elsewhere [5, 36]. The steroid therapy regimen was the same as discussed above for arteritic AION.

Non-arteritic PION

In a "patient choice" study [43], I investigated high-dose systemic corticosteroid therapy during very early stages of PION in 32 eyes. Of them, 16 opted for treatment and 16 for no treatment. There was a significant improvement in the treated group compared to the untreated group in visual acuity (p=0.023) and in visual field defect (p=0.030). The steroid therapy regimen was the same as discussed above for NA-AION.

Surgical PION

No treatment has been found to be effective to recover or improve the lost vision in these cases. Therefore, it is essential to take prophylactic measures during surgery, to minimize the risk of its development. These include: avoiding arterial hypotension, excessive fluid replacement and hemodilution, pressure on the eyeball and orbit, and dependent position of the head, as well as shortening the duration of surgery to the minimum. Since systemic cardiovascular risk factors may predispose a patient to a higher risk of developing surgical PION, it may be advisable to consider those factors in the decision to perform surgery.

Conflict of interest The author has no conflict of interest of any kind.

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