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EDITORIAL

# Non-arteritic anterior ischemic optic neuropathy and thrombophilia

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Non-arteritic anterior ischemic optic neuropathy (NA-AION) is a common, visually disabling disorder occurring in the middle-aged and elderly, but no age group is immune to it—in two large series the youngest persons with NA-ION were 18 [1] and 13 [2] years old. NA-AION is a multifactorial disease; several risk factors play a role in its development, some acting as predisposing and others as precipitating risk factors, as discussed detail elsewhere [3–6]. Some studies have mentioned thrombophilia [7–12] as a risk factor, including one published in this issue of this journal [13]. To place the role of thrombophilia in proper perspective, it is essential to discuss two basic issues, i.e., the pathogenesis of NA-AION and whether thrombophilia has any role in that or not.

## Pathogenesis of NA-AION

One often hears and reads that the pathogenesis of NA-AION is unknown, but that is no longer true with our current knowledge of the subject. The pathogenesis of NA-AION is discussed at length elsewhere [4]. NA-AION represents a multifactorial acute ischemic disorder of the optic nerve head (ONH) which is supplied by the posterior ciliary artery.

There is a widespread belief among ophthalmologists and neurologists that NA-AION has a pathogenesis similar to that of a stroke, i.e., both being thromboembolic disorders; however, the evidence does not support this view.

1. First and foremost, fluorescein fundus angiography soon after the onset of NA-AION shows only a delayed and slow filling of the peripapillary choroid and/or choroidal watershed zones, but no permanent occlusion [14], whereas a thromboembolic occlusive disorder (such as arteritic AION [14]) is always associated with complete occlusion of the posterior ciliary artery supplying the ONH.
2. The severity of ONH ischemic damage depends upon the severity and duration of the ONH ischemia, and that determines the extent of recovery of visual function following the acute episode. The following provides the important relevant information on this subject.

A. Our studies have shown that in the vast majority of NA-AION patients, the main factor precipitating the development of NA-AION is transient nonperfusion or hypoperfusion of the ONH circulation during sleep in persons with other predisposing risk factors [4, 15]. This is supported by the following:

(i) A study of 925 episodes of NA-AION showed that, in 73% of the episodes, the patients first discovered visual loss upon awakening or at first opportunity to use vision critically after sleeping [15]. This indicates that nocturnal arterial hypotension precipitated the development of NA-AION in persons with other risk factors; most of the other patients could not recollect definitely time when they first discovered the visual

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loss, suggesting that the visual loss development during sleep may be much higher than 73%.

(ii) Twenty-four-hour ambulatory blood pressure monitoring showed not only a marked fall of blood pressure during sleep (Fig. 1) but also a significant relationship between progressive visual field deterioration and nocturnal arterial hypotension in NA-AION [16, 17].

(iii) Among about 1,500 patients with NA-AION whom I have seen over the years, I have from time to time seen patients whose NA-AION was precipitated by the patient starting to take an arterial hypotensive medication in the evening or bedtime, producing abnormal nocturnal arterial hypotension [17]. There is evidence to suggest that the development of NA-AION following the use of erectile dysfunction drugs is primarily caused by fall of blood pressure in persons in the presence of other risk factors [18, 19].

A transient fall of blood pressure during sleep results in a fall of perfusion pressure (perfusion pressure = mean blood pressure minus intraocular pressure) in the ONH vessels, causing transient nonperfusion or hypoperfusion of those vessels. A fall in perfusion pressure in the capillaries of the ONH below the critical autoregulatory range level, in susceptible persons, results in ischemia of the ONH and development of NA-AION. The severity of ONH ischemia following transient nonperfusion or hypoperfusion may vary from mild to marked, depending upon the severity and the duration of the transient ischemia and other factors influencing the blood flow in the ONH [20].

B. In NA-AION, because there is only transient nonperfusion or hypoperfusion in the ONH circulation, there is usually much less severe and less extensive ONH damage than in arteritic AION due to thrombotic occlusion of the posterior ciliary artery [21]. Two large studies [22, 23] have shown that 41% of NA-AION eyes show spontaneous visual acuity improvement. In sharp contrast to that, no such visual improvement is seen in arteritic AION (a thrombotic disorder) [24].

Thus, the available evidence indicates that NA-AION is usually **NOT** a thromboembolic disorder but is due to a transient fall of perfusion pressure in the ONH vessels during nocturnal arterial hypotension, which results in transient nonperfusion or hypoperfusion of those vessels.

Further proof that NA-AION, unlike stroke, is not a thromboembolic disorder is provided by the following:

(i). While there is a significant association between smoking and cerebrovascular accident (a thromboembolic disorder) [25], no such association has been found between smoking and NA-AION [1, 26].

(ii). While the beneficial effect of aspirin in cerebrovascular accident (a thromboembolic disorder) is well-established, studies have shown that aspirin has no beneficial effects in NA-AION (being a hypotensive disorder) [26–28].

There is highly prevalent misconception in the ophthalmic community that a small or absent cup is actually the primary factor in the development of NA-AION; this has resulted in catchy terms like “disc at risk”. The role of an absent or small cup in the pathogenesis of development of NA-AION is discussed in detail elsewhere [29, 30]. Briefly, in the multifactorial scenario of the pathogenesis of NA-AION, an absent or small cup is simply a secondary contributing factor, **ONCE** the process of NA-AION has started, and **NOT** a primary factor [29, 30].

Thus the pathogenesis of NA-AION is complex but not, as often stated, unknown.

## Thrombophilia

Thrombophilia is an inherited or acquired predisposition to thrombosis [31]. To evaluate whether thrombophilia has

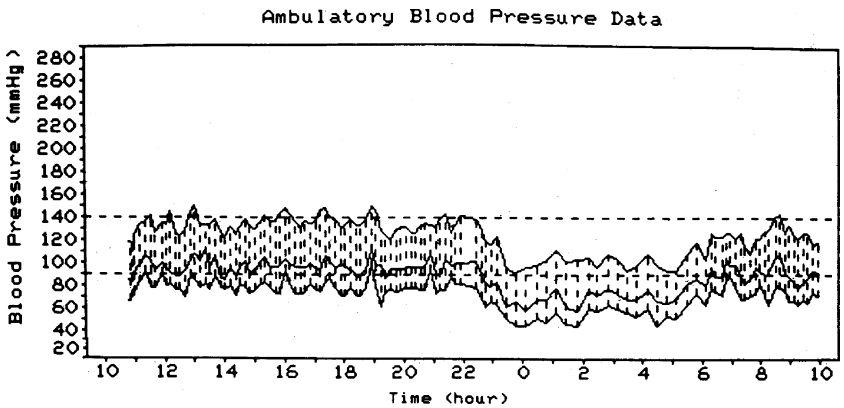


**Fig. 1** Ambulatory blood pressure monitoring records (based on individual readings) over a 24-hour period starting from about 11 A.M., in a 58-year old woman with bilateral NA-AION, and on no medication. The blood pressure is perfectly normal during the waking hours but there is marked nocturnal arterial hypotension during sleep

any role in development of NA-AION, one has to consider the following facts.

1. Thrombophilic factors cause circulatory disorders by causing thrombosis. However, as discussed about, NA-AION in the vast majority is **NOT** a thrombotic disorder.
2. The principal clinical manifestation of thrombophilia is venous thromboembolism [31]. NA-AION is not a venous thrombotic disorder but an arterial ischemic disorder.
3. As discussed above, aspirin, which is effective in treating thromboembolic disorders, has been shown to have no protective effect in NA-AION [26–28].
4. There are studies that have shown no association between NA-AION and thrombophilic risk factors. For example, Salomon et al. [32] in 61 patients with NA-AION found no association with Protein C, protein S, antithrombin III, lupus anticoagulant, and three prothrombotic polymorphisms (i.e., factor V G1691A, factor II G20210A, and methylenetetrahydrofolate reductase [MTHFR] C677T). Similarly, Biousse et al. [33] in 14 patients with NA-AION found homocysteine within normal limits in all of them, and mutation positive and mutation negative patients for MTHFR C677T did not differ with respect to clinical data concerning risk factors for NA-AION. Both studies concluded that there was no association between NA-AION and thrombophilic risk factors.

If testing of NA-AION patients reveals the presence of one or more abnormal thrombophilic factors that does not automatically imply a cause-and-effect relationship. That may be purely a coincidental finding and may explain some of the reported positive findings.

Thus, in the light of the above facts, there is little evidence that thrombophilia plays a role in development of NA-AION in the vast majority of cases. Of course, the possibility that thrombophilia may be involved in a rare case cannot be ruled out—in medicine there is no such thing as "never". That raises the important question whether all patients with NA-AION should be tested for thrombophilia, as advocated by some [13]. According to Heit [31], "Currently, there is no single laboratory assay or simple set of assays that will identify all thrombophilias. Consequently, a battery of complex and potentially expensive assays is usually required. Many of these laboratory analyses are affected by other conditions (e.g., warfarin reduces protein C and S levels) such that the correct interpretation of the results can be complicated and always requires clinical correlation." Leiden mutation of the factor V gene is associated with a procoagulant state, especially in the venous bed, and its association with arterial thrombotic disease remains unclear. Thus, testing patients with NA-AION for thrombophilia is unwarranted, unless there is a medical or family history of thrombosis.

Among the various studies on thrombophilia in NA-AION claiming an association between NA-AION and thrombophilia, there is not only conflicting and contradictory information but also there are other problems. Following are some examples:

1. The study by Giambene et al. [13], published in this issue, reported plasma levels of homocysteine and lipoprotein(a) significantly higher in patients with NA-AION compared with controls, with no significant difference in MTHFR C677T polymorphism between the two groups. They found arterial hypertension and dyslipidemia significantly more prevalent in patients than in controls, but that was not the case with diabetes mellitus and smoking. Their findings that there was no difference in prevalence of diabetes between the control and NA-AION groups in their study conflicts with the well-established fact that diabetes is significantly more common in NA-AION than controls [3, 5, 6]. This fact indicates a serious problem with the type of patients in the study and indirectly, the validity of their other findings. The authors also state that they did not register nutritional habits of their patients—which would be important to determine the role of diet on vitamin B6 and homocysteine circulating values. Nor did they measure homocysteine post-methionine plasma levels, which could be useful to reveal an impairment of homocysteine metabolism in a number of subjects. Their findings of significantly higher homocysteine in patients with NA-AION compared with controls is contradicted by the study by Biousse et al. [33], who found no such difference. Thus, one has to interpret the claims of Giambene et al. [13] in the light of these limitations, with caution.
2. Misleading information can be the result of several other factors. When diseases that look superficially very similar occur in different organs, there is a strong tendency to assume that the diseases pathogenesis and management are the same in the different organs. This is how the pathogenesis and management of stroke has been extrapolated to NA-AION. This represents a serious error of judgment. Similarly, the pathogenesis and management of central retinal vein occlusion and deep vein thrombosis are usually considered similar, although they have nothing in common morphologically, pathologically or clinically except for the thrombus. Also, some studies have lumped together all kinds of ocular vascular occlusive diseases in their thrombophilic evaluations, as if they were pathogenetically all one clinical entity. For example, Pianka et al. [8] and Stanger et al. [34] combined NA-AION with retinal

vascular occlusions in their study on thrombophilia, which is unwarranted because that comprises at least five distinct ocular vascular disorder, with very different pathogeneses and other basic aspects.

These and other similar issues result in not only misleading information but also controversy on the pathogenesis and management of various diseases.

Studies have shown that severe hyperhomocysteinemia is a risk factor for development of atherosclerosis [35] and arteriosclerosis [36]. As discussed above, NA-AION is a disease of the middle-aged and elderly, a population in which there is a high incidence of atherosclerosis, arteriosclerosis, hyperlipidemia, diabetes mellitus, and other cardiovascular and other systemic diseases [3, 4]. Thus, finding of hyperhomocysteinemia in some NA-AION patients may simply be a manifestation of those vascular disorders and not in any way related to NA-AION.

## Conclusions

In the light of all the available evidence, there is no scientifically rational basis for believing that thrombophilia has any role to play in NA-AION. Thus, testing patients with NA-AION for thrombophilia is unwarranted, unless there is a definite medical or family history of thrombosis.

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