THE SPECTRUM OF OPTIC DISC ISCHEMIA IN PATIENTS YOUNGER THAN 50 YEARS (AN AMERCIAN OPHTHALMOLOGICAL SOCIETY THESIS)

By Anthony C. Arnold MD, Roberta M. S. Costa MD, and Oana M. Dumitrascu MD

ABSTRACT

Purpose: To identify the spectrum of clinical and fluorescein angiographic features of optic disc ischemia in patients younger than 50 years.

Methods: This retrospective comparative case series from a university consultative neuro-ophthalmology practice consisted of two phases. The first compared 108 cases of nonarteritic anterior ischemic optic neuropathy in patients younger than 50 years (NAIONy) to a cohort of 108 cases in patients 50 years or older (NAIONo). Predisposing risk factors, fluorescein angiographic features, and clinical course were compared. In the second phase, 12 cases of diabetic papillopathy under age 50 were assessed by fluorescein angiographic criteria for evidence of optic disc ischemia and compared to patients with NAIONy.

Results: NAIONy comprised 108 (12.7%) of 848 NAION cases reviewed. Chronic renal failure with dialysis and migraine were more common in NAIONy. Fellow eye involvement rate was significantly higher for NAIONy patients (46/108, 42.6%) than for NAIONo patients (32/108, 29.6%). Fluorescein angiographic features of ischemia were documented in 44 (81.5%) of 54 eyes studied. In one case, these features were documented in pre-NAION edema. Diabetic papillopathy demonstrated delayed filling consistent with ischemia in 7 of 10 (70.0%), without significant visual field loss.

Conclusions: Ischemic optic neuropathy in patients younger than 50 years is not rare. Fellow eye involvement is more frequent in younger patients. Fluorescein angiography confirmation of impaired perfusion in multiple syndromes of optic neuropathy corroborates a spectrum of optic disc ischemia ranging from perfusion delay without visual loss to severely impaired perfusion and visual loss and incorporates optic neuropathies previously considered nonischemic.

Trans Am Ophthalmol Soc 2013;111:93-118

INTRODUCTION/BACKGROUND

Nonarteritic anterior ischemic optic neuropathy (NAION) most frequently occurs in patients aged 50 years or older. The mean age at onset in most studies ranges from 57 to 65 years, although many, such as the Ischemic Optic Neuropathy Decompression Trial (IONDT), may bias the data by excluding patients under the age of 50. The disorder has been characterized by the following distinctive features[1]:

1. Acute or subacute onset of visual loss, usually monocular at onset, involving the inferior visual field (altitudinal loss) most commonly (Figure 1), but any pattern of field loss consistent with optic nerve origin may occur
2. Single episode of visual loss in the majority, with a minority progressively worsening over weeks before stabilizing
3. Absence of pain or mild nonspecific pain (without eye movement) associated
4. Occurrence in "crowded discs" (small diameter and small cup-disc ratio as measured in the fellow eye) (Figure 2)
5. Optic disc edema at onset and probably prior to onset of visual field loss
6. Diffuse (Figure 3, upper left) or segmental (Figure 3, upper right) pattern of either superior or inferior localized edema, sometimes with a sharply demarcated horizontal linear border
7. Occasional prominent optic disc surface vascular dilation (Figure, 3 lower left)
8. Superimposed development of optic disc pallor over weeks, with the appearance of "pale swelling" (Figure 3, lower right) replacing hyperemic edema, later evolving into optic atrophy
9. Optic atrophy, which may be diffuse (Figure 4, left) or may show a sharply segmental or altitudinal (Figure 4, right) configuration
10. Visual loss, which is usually permanent and stable, but with a substantial spontaneous improvement rate for visual acuity (42.7% improved by ≥3 lines Snellen acuity at 6 months in the IONDT)
11. Unusual recurrence in the same eye
12. Fellow eye involvement in a minority

THESIS HYPOTHESIS

Based on our prior study of fluorescein angiography in ischemic and nonischemic optic neuropathies and our preliminary observations in younger patients with acute optic neuropathies, we postulated that in patients under age 50:

1. NAION
    a. is not rare;
    b. demonstrates fluorescein angiographic features consistent with optic disc ischemia;
    c. has a higher rate of fellow eye involvement than NAION age 50 or older; and
    d. is associated with a different vasculopathic risk factor profile than NAION age 50 or older.
2. Pre-NAION optic disc edema and the syndrome of diabetic papillopathy both
    a. demonstrate fluorescein angiographic features consistent with optic disc ischemia and
    b. represent syndromes of ischemia with minimal or reversible optic nerve dysfunction, without infarction.

From the Division of Neuro-Ophthalmology, Jules Stein Eye Institute, Department of Ophthalmology, University of California, Los Angeles.

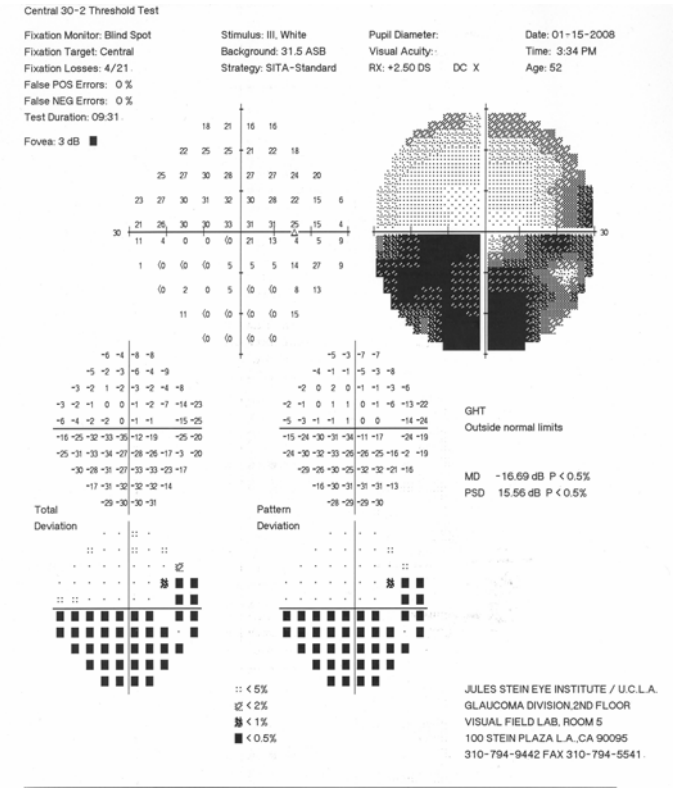

FIGURE 1

Visual field in nonarteritic anterior ischemic optic neuropathy in older patients (NAIONo). Quantitative perimetry shows inferior altitudinal visual field defect in right eye.

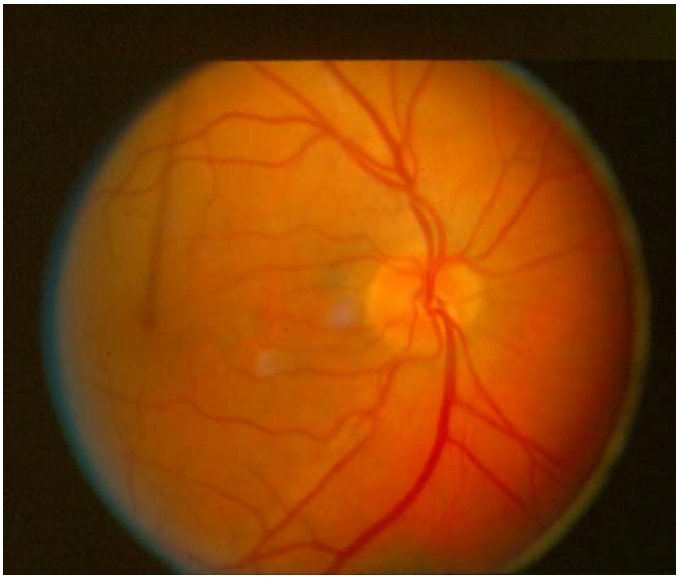

FIGURE 2

Fundus photograph showing fellow eye in nonarteritic anterior ischemic optic neuropathy in older patients (NAIONo). Optic disc is small in diameter, with cup-disc ratio <0.2.

The background and rationale for these hypotheses follows.

EVIDENCE FOR ISCHEMIA

The specific pathophysiology of NAION remains elusive. Features are similar to arteritic (due to giant cell arteritis) AION, in which the vasculopathy has been documented to be secondary to inflammation and thrombosis within the short posterior ciliary artery (SPCA) circulation to the optic disc.[2-4] These findings, along with the prevalence of vasculopathic risk factors in the majority of NAION patients, suggest an ischemic origin, but clear documentation of the locus of vasculopathy has been lacking. There are only a handful of histopathologically documented infarcts of the optic nerve head in clinically proven NAION; eight cases have been reported, and many of these were atypical.[5-10] Knox and associates' large series of 193 histopathologically proven optic disc infarcts[11] had no correlated clinical information, so we do not know what percentage of these had a clinically confirmed NAION syndrome. We have no histopathologically documented occlusion of the SPCA or its tributaries in NAION, and we do not possess the technology to directly image in vivo the microvascular supply to the retrolaminar and laminar optic nerve head in order to confirm either pre-episode vascular narrowing or intra- or post-episode occlusion within this system. Color Doppler flow studies have been used to study the SPCA circulation in NAION, but the technique is limited to flow velocity, has significant sources of error, and provides insufficient resolution to document stenosis.[12,13] Laser Doppler flow studies image primarily the disc surface microcirculation derived from the central retinal artery, not the SPCA tributaries that supply the deeper layers of the disc, which suffer infarction.[14]

The best evidence of optic disc ischemia remains fluorescein angiography (FA). When applied to the earliest phases of dye appearance in the eye, the technique allows visualization of the sequential perfusion of the vascular beds of the choroid, retina, and both deep (prelaminar) and inner surface of the optic disc (Figure 5). Several investigators previously reported compromise of optic disc filling on FA, but criteria for abnormally delayed filling, which would suggest ischemia, were not developed.[15,16] More recently, Arnold and Hepler[17] performed a systematic analysis of the FA filling characteristics of patients with acute (within 3 weeks of onset, disc edema present without optic atrophy) NAION and compared findings to controls. In normal eyes, the prelaminar optic disc fills with the choroid and before the central retinal artery, which supplies flow (and fluorescein filling) to the inner disc layers (Figure 5). A significant delay of filling of 5 seconds after initial choroidal filling was present in all or a portion of the prelaminar layer of the optic disc, but not consistently in the peripapillary choroid (Figures 5 and 6), in 75.6% of patients. In 53.7% of these, a focal region of

early disc hyperfluorescence, derived from the retinal rather than the posterior ciliary arterial circulation, was seen. This contrasted with the pattern documented by both Mack and associates[18] and Siatkowski and associates[19] for arteritic AION, which showed severe diffuse filling delay of both disc and choroid, suggesting flow impairment at the level of the SPCA prior to the bifurcation into parapapillary and choroidal branches. The significance was that the microcirculatory impairment in NAION must be more distal, affecting the branches to the disc while often sparing those to the choroid. Arnold and associates[20] subsequently studied the FA filling characteristics of patients with optic disc edema from nonischemic causes such as papillitis and papilledema and found that 0 of 16 cases demonstrated significant delay (Figure 7). These data indicated that the filling delay in NAION was primary and not secondary to a mechanical obstruction from the optic disc edema itself.

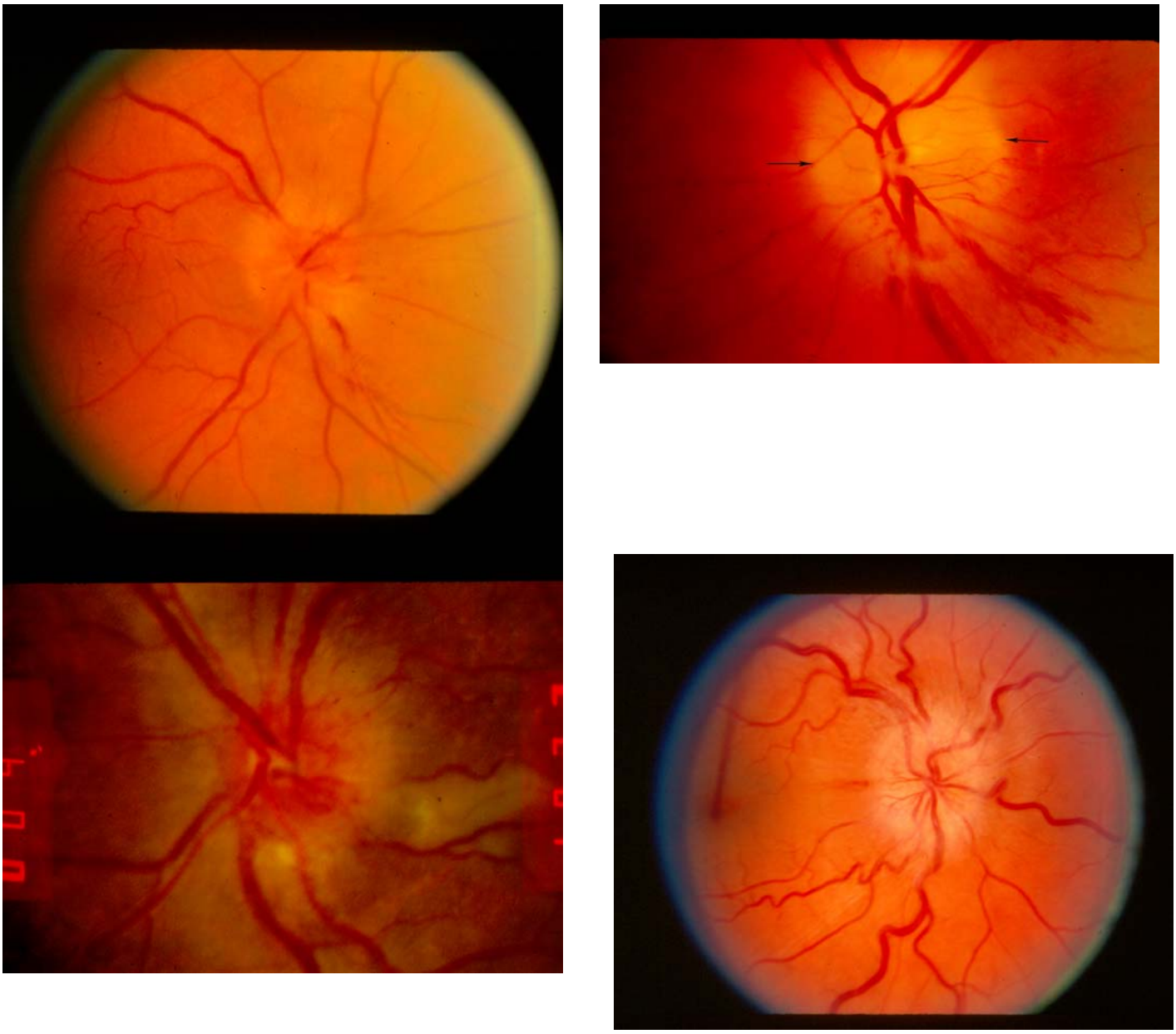

FIGURE 3

Fundus photograph showing disc edema in nonarteritic anterior ischemic optic neuropathy in older patients (NAIONo). Upper left, Optic disc with diffuse edema and adjacent flame hemorrhage. Upper right, Optic disc with segmental edema worse inferiorly below arrows. Lower left, Optic disc with dilated surface vessels. Lower right, Optic disc with pale edema.

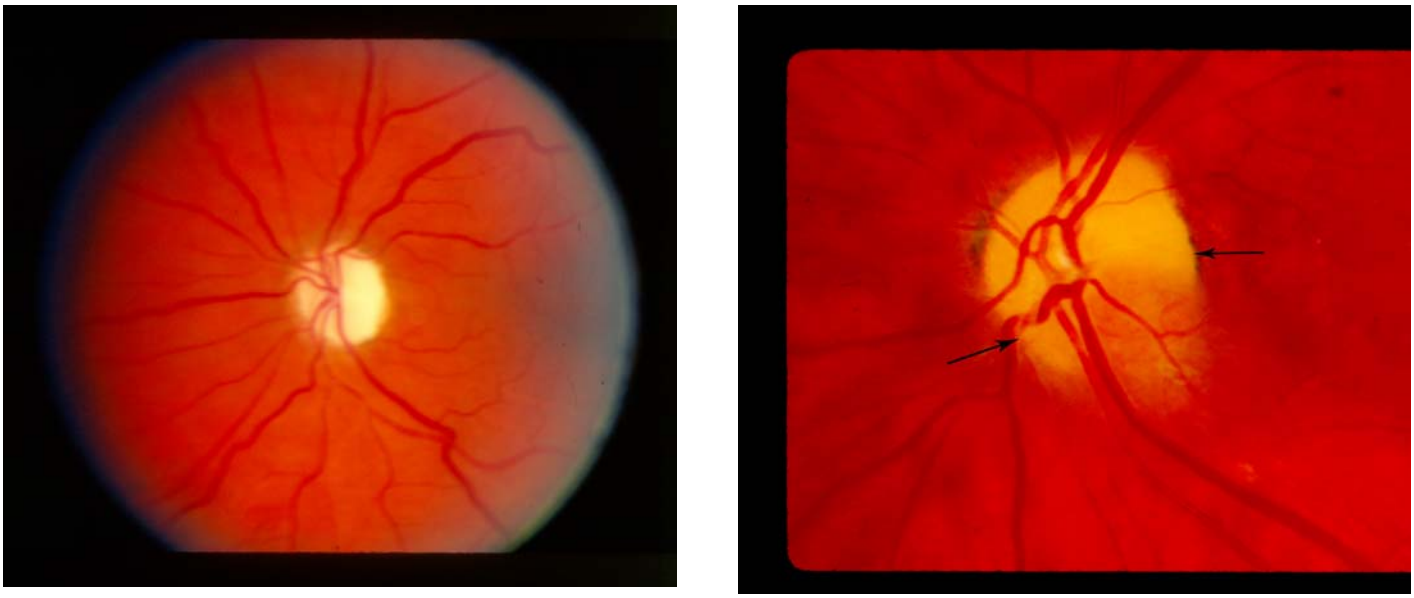

FIGURE 4

Fundus photograph showing optic atrophy in nonarteritic anterior ischemic optic neuropathy. Left, Optic disc with diffuse atrophy. Right, Optic disc with segmental atrophy above arrows.

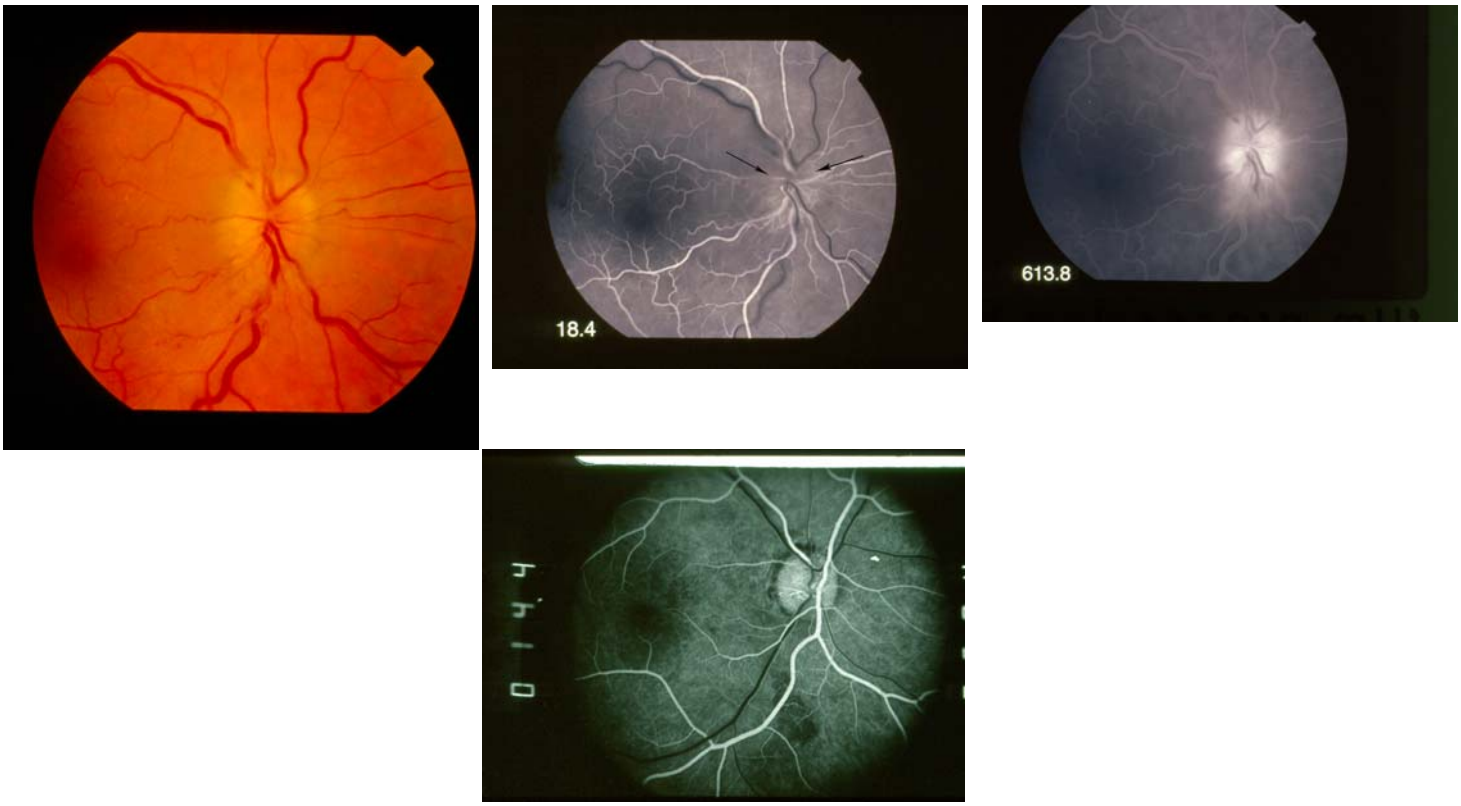

FIGURE 5

Fluorescein angiography in nonarteritic anterior ischemic optic neuropathy diffuse. Upper left, Fundus photograph showing diffuse optic disc edema. Upper middle, Fluorescein angiogram, early arteriovenous phase, showing diffusely poor filling of optic disc (arrows) at 18.4 seconds. Upper right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 613.8 seconds. Lower, Fluorescein angiography, early arteriovenous phase in normal eye, showing normal diffuse filling of the optic disc at 14.4 seconds

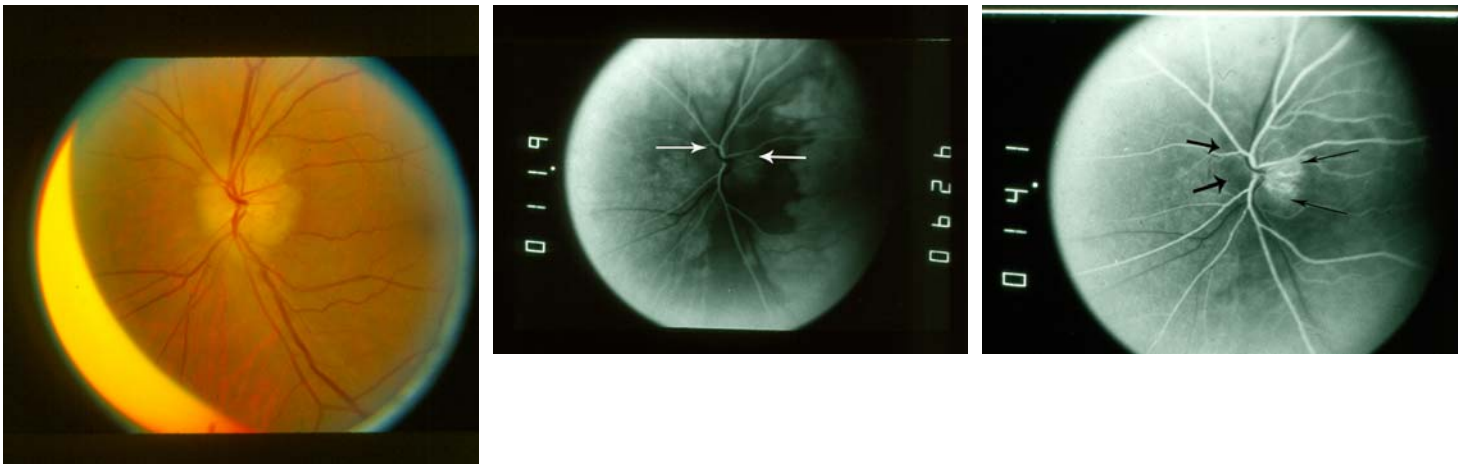

FIGURE 6

Fluorescein angiography in nonarteritic anterior ischemic optic neuropathy segmental. Left, Fundus photograph showing diffuse optic disc edema. Middle, Fluorescein angiogram, early phase, showing diffusely poor filling of optic disc at 11.9 seconds (arrows). Right, Fluorescein angiogram, early arteriovenous phase, showing poorly filling optic disc (short arrows, left) with relatively spared segmental region of early filling at 14.1 seconds (long arrows, right) .

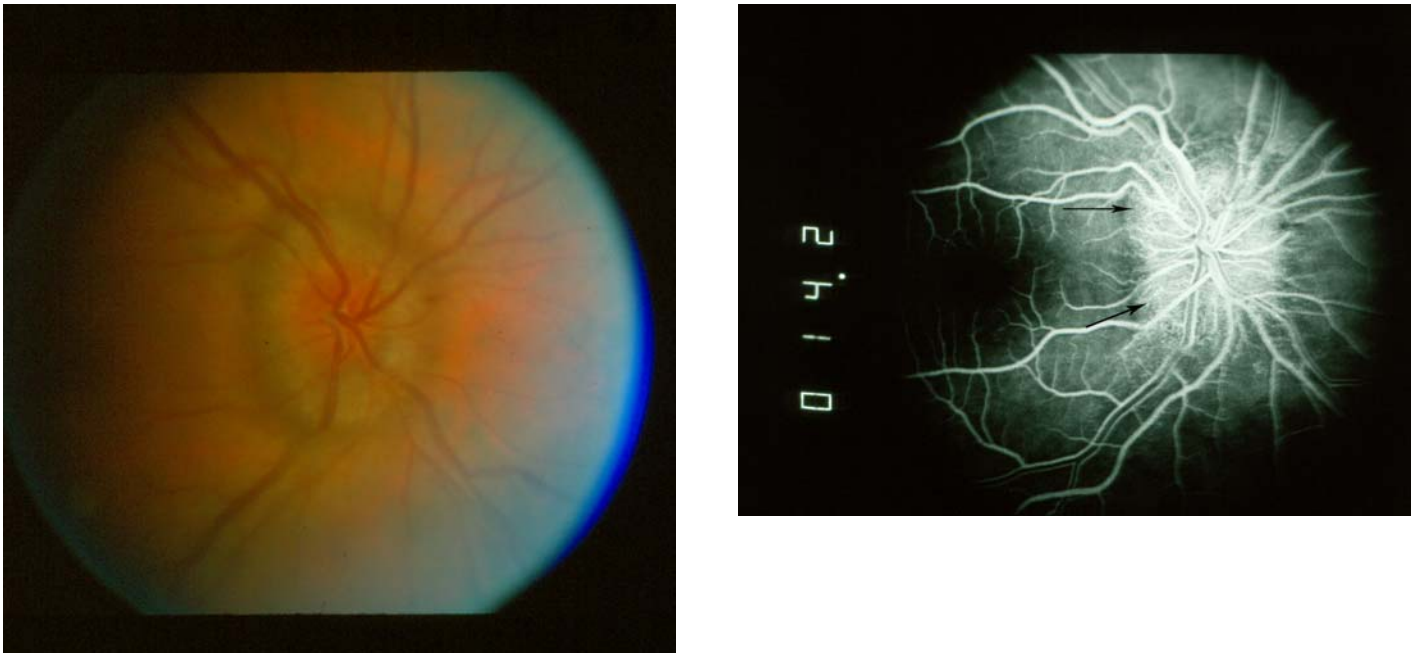

FIGURE 7

Fluorescein angiography in nonischemic optic disc edema. Left, Fundus photograph showing diffuse optic disc edema. Right, Fluorescein angiogram, early arteriovenous phase, showing complete filling of optic disc (arrows) at 14.2 seconds.

RISK FACTORS

Virtually every series of patients with NAION confirms that the so-called crowded disc (small diameter, cup-disc ratio <0.2) is present in a large majority, suggesting that this structure plays a role in pathogenesis.[21-24] The precise mechanism by which it contributes, however, remains unclear. Most investigators propose that the relatively inflexible region of the lamina cribrosa provides the setting for a compartment syndrome within the optic nerve head. In the setting of microcirculatory insufficiency and developing ischemia, the combination of both mechanical and ischemic axoplasmic flow stasis, with resultant intracellular axonal swelling, may further compress the microcirculation and produce a vicious cycle of ischemia and compression. This feature has been implicated in two histopathologic studies. Tesser and associates[10] reported that the infarct documented in their case did not follow a specific vascular territory, suggesting a compartment syndrome as a mechanism. Knox and associates[11] demonstrated cavernous degeneration within the laminar region in 36% of eyes in their series of 193 optic nerve infarctions, a number of which showed substantial compression of the adjacent axons by the expanding mucopolysaccharide cavern, lending support to the compartment syndrome theory.

NAION has been reported in association with many conditions that may predispose to decreased optic nerve head perfusion via

microvascular occlusion. Systemic hypertension was documented in 34% to 49% of patients[25-27] (47% in the IONDT[28]); however, in several of the studies that compared these figures to matched population data from the National Health Survey,[26,27] statistical significance was reached only in the younger age-group, 45 to 64 years. Hayreh and associates,[29] in contrast, found a significantly increased prevalence in all age-groups. Diabetes was reported in 5% to 25% (24% in the IONDT[28]), with statistically significant increased prevalence in all ages in all but one study.[25-27,29] Diabetes was associated with the development of NAION at a younger age in most series as well.

Recent studies have addressed additional vasculopathic risk factors. Jacobson and associates[30] performed a case-control study in NAION, addressing hypertension and diabetes, along with smoking and hypercholesterolemia, in 51 patients compared with two separate control groups. While hypertension was found in 57% of patients, it was not found to be significantly more prevalent than controls in any age-group; however, diabetes, found in 34%, was a significant risk factor in all age-groups. Neither hypercholesterolemia nor smoking demonstrated significant risk. The 61-patient case-control study of Salomon and associates[31] also confirmed diabetes but not hypertension as a risk factor; hypercholesterolemia was found to be significant, but smoking was not. Two other case-control studies of risk factors have addressed the issues of hyperlipidemia and smoking[32,33]; hypercholesterolemia was a significant risk in both, whereas hypertriglyceridemia and smoking were linked in a limited number studied. A large-scale (137 cases) but uncontrolled study by Chung and associates[34] concluded that smoking was a significant risk factor on the basis that smokers developed NAION at a significantly younger age than nonsmokers. Deramo and associates[35] reported a series of 37 patients with NAION presenting before the age of 50, in which mean serum cholesterol was significantly elevated when compared with age- and gender-matched controls (235.4 vs 204.0 mg/dL).

Elevated plasma homocysteine levels have been associated with an increased risk of premature ischemic events (peripheral vascular disease, stroke, myocardial infarction) in patients under 50. The relation to NAION remains unclear, as a limited number of studies with small patient numbers have reported widely varying results, from 0 of 14 NAION cases under age 50 with hyperhomocysteinemia (Biousse and associates[36]) to 18 (45%) of 40 NAION patients with hyperhomocysteinemia vs 9.8% of controls (Pianka and associates[37]).

Salomon and associates[31] have studied prothrombotic risk factors, including lupus anticoagulants, anticardiolipin antibodies, prothrombotic polymorphisms (factor V Leiden), and deficiencies of protein C, S, and antithrombin III in a series of 61patients with NAION vs 90 controls, finding no correlation with any of these factors. They did, however, find evidence of platelet glycoprotein polymorphisms in a series of 92 NAION patients vs controls, with second eye involvement more frequent and earlier in onset in those with the polymorphism.[38]

NAION has been reported in patients with migraine, often occurring below age 50, some in the third decade.[39,40] The mechanism of vasculopathy has been postulated to be vasospasm. No systematic study of migraine as a risk factor in NAION has been performed.

CLINICAL COURSE

Ipsilateral Recurrence

After stabilization of vision, usually within 2 months, recurrent episodes of visual loss in an affected eye are unusual. Repka and associates[26] reported recurrent episodes in only 3 (3.6%) of 83 patients. Hayreh and associates[41] reviewed 829 eyes in 594 consecutive patients with NAION for evidence of recurrent events in the same eye occurring at least 2 months after initial onset. Recurrence was documented in 53 eyes (6.4%).

Fellow Eye Involvement

Eventual involvement of the contralateral eye has been reported in from 24% to 39% of early series, with varying and uncontrolled follow-up.[26,42-45] Two large-scale systematic analyses have produced remarkably similar results. Beck and associates[46] reviewed 431 patients with NAION, finding a 5-year cumulative probability for fellow eye involvement of 19%; of the 643 patients in this study originally screened, 154 were excluded because they had prior NAION in the fellow eye, bringing the total of bilateral cases to 202 (31.4%). In the IONDT,[47] fellow eye involvement at 5 years was estimated at 14.7%; of the 418 patients enrolled, NAION in the fellow eye was present in 80 patients at baseline, bringing the total of bilateral cases to 128 (30.6%). Diabetes was associated with a higher risk of fellow eye involvement.

NAION IN YOUNG PATIENTS (NAIONY)

Differentiation From Optic Neuritis

NAION, particularly in patients under 50 years of age, must be differentiated from idiopathic demyelinative optic neuritis, vasculitic or infectious optic nerve inflammation, infiltrative optic neuropathies, and anterior orbital lesions producing optic nerve compression. Optic neuritis may resemble ischemia with regard to rate of onset, pattern of visual field loss, and optic disc appearance; however, in most cases, the patient's younger age, pain with eye movement, and early recovery make distinction clear. In cases of inflammation and infiltration, intraorbital optic nerve swelling and enhancement are frequently seen on magnetic resonance imaging (MRI), whereas the nerve appears normal in NAION. Optic nerve inflammation associated with syphilis or sarcoidosis often is associated with other intraocular inflammatory signs. Orbital lesions producing disc edema usually are associated with gradually progressive visual loss, but occasionally onset is more rapid. Subtle signs of orbital disease, including mild proptosis, lid or eye movement abnormalities, or the persistence of optic disc edema past the usual 4 to 6 weeks in NAION, are usually present. As noted above, FA is an accurate tool to distinguish ischemic from nonischemic optic disc edema.

Prior Reports of NAIONy

Although isolated patients under age 50 were included in early series of NAION, reports focusing on NAION in young patients date to the early 1980s, when a syndrome of recurrent episodes of acute optic neuropathy was described.[48-50] Many patients were younger than the typical patient with NAION, although the majority were over age 50. However, the three cases reported by Dutton and Burde[51] ranged in age from 17 to 27, and one report by Hamed and associates[52] included a 36-year-old patient. Recurrent episodes in the ipsilateral eye were a hallmark feature of these cases and ranged from three to four events. The cases were presumed to be ischemic based on the clinical findings of lack of pain, segmental disc edema with flame hemorrhage, altitudinal pattern of visual field loss, and lack of recovery, but no FA to confirm impaired perfusion or MRI to rule out optic nerve inflammation was performed. The occurrence of NAION in patients under age 50 was felt to be rare.[53]

Isolated reports of NAION in patients under age 50 followed. Deramo and associates[35] identified 43 (7.5%) of 577 cases of NAION under age 50, comparing them with regard to vasculopathic risk factors to a control group of age- and gender-matched patients without NAION. Hyperlipidemia (including cholesterol, low-density lipoprotein, and triglycerides) and diabetes were significantly more frequent in the NAION patients than controls. Bilateral involvement occurred in 14 of 37 (37.8%). Twenty-four cases underwent MRI, with none showing evidence of optic nerve inflammation. The issue of recurrence was not addressed. Janaky and associates[54] subsequently described three cases, all diabetic, who suffered acute optic neuropathies with disc edema consistent with NAION. All were bilateral and all demonstrated crowded optic discs. Although the report indicates recurrence in each case, in two of the three, only a single episode occurred in each eye; in the third case, two episodes occurred in each eye over several years.

The most comprehensive study of this patient group was reported in 2007 by Preechawat and associates.[55] They reviewed 727 consecutive patients with NAION, finding 169 (23.2%) under the age of 50. Magnetic resonance imaging was performed in all cases, and imaging evidence of optic nerve inflammation was an exclusion criterion. Crowded discs were noted in 189 (82%) of 230 eyes. Chronic renal failure and dialysis was noted in 8 of 169 (4.7%). Bilateral involvement occurred at initial evaluation in 17 cases (10%), increasing to 70 cases (41%) at median follow-up of 7 months. Of those with observed fellow eye involvement after initial presentation (53/152 [35%]), the median time to second eye involvement was 12 months. Anemia and type 1 diabetes were significantly associated with fellow eye involvement. Recurrence was found in 11 eyes (5.9%). Twenty-six percent of patients (44/169) had no risk factors other than crowded discs. Hypercoagulable state was noted in 9 patients (5%), 3 of which had hyperhomocysteinemia; antiphospholipid antibodies were documented in 5 patients. Neither FA confirmation of ischemia nor a control population of patients aged 50 or older with NAION was included in this study.

OPTIC NEUROPATHY IN CHRONIC RENAL FAILURE AND DIALYSIS

A syndrome of acute optic neuropathy in patients on dialysis for chronic renal failure (CRF) has been described, but the definition has been unclear. Optic neuropathy occurring in this setting may represent malignant hypertension and elevated intracranial pressure, extensive retinopathy with posterior pole edema including the optic disc, a true toxic optic neuropathy secondary to uremia, or NAION. Accelerated development of vascular disease in these patients places them at risk for optic disc ischemia, and several cases have been reported as AION, even in the very young.[56-60]

The term *uremic optic neuropathy* has been used to describe acute optic nerve dysfunction and disc edema in patients with renal failure. Knox and associates[61] reported substantial visual improvement in 5 of 6 patients with optic neuropathy and uremia who underwent immediate dialysis and corticosteroid therapy. Saini and associates[62] also reported severe bilateral optic neuropathy in a uremic patient, which did not initially respond to steroid therapy, but improved dramatically following hemodialysis, 3 to 4 weeks after onset of visual symptoms. The temporal relation of visual improvement to reduction of uremia in these cases suggests a causative role for metabolites related to renal failure. Hamed and associates[57] reported 3 cases of optic neuropathy and uremia in patients 40 to 61 years of age, and postulated sequential AION in 2, which did not improve on steroid therapy and hemodialysis. The third patient improved after discontinuing deferoxamine.

The accelerated diffuse vasculopathy that occurs in patients with CRF may predispose to optic disc ischemia. In those with chronic hypertension, impaired autoregulation of SPCA blood flow due to hyalinosis and alteration in vascular tone may limit the ability of the optic nerve head to withstand blood pressure fluctuations.[63,64] The rapid and sometimes profound changes in fluid volume and blood pressure related to dialysis may play a role. Finally, superimposed chronic hypotension and anemia may lower optic disc perfusion pressure and oxygen delivery.[65] Servilla and Groggel[56] reported a case of AION in a uremic patient, which occurred secondary to an acute hypotensive episode (blood pressure, 40/0) during hemodialysis. Reports by Michaelson and associates[58] and Connolly and associates[60] describe four cases of presumed AION in patients with CRF, hypotension, and anemia, in patients aged 23, 25, 26, and 39. Acute hypotension was reportedly a precipitating factor in two of these cases, and partial visual recovery was attributed to correction of low perfusion pressure. In a third case, and in four cases in children aged 9½ to 11 described by Taylor and associates,[63] AION was attributed to excessively rapid reversal of hypertension.

Of the early reported cases cited above, 19 of 24 (79.2%) demonstrated bilateral simultaneous optic neuropathy. In the series of Preechawat and associates,[55] 6 of 8 patients with CRF had bilateral involvement.

OPTIC DISC ISCHEMIA WITHOUT INFARCTION

Pre-NAION Ischemic Edema

Optic disc edema has been documented in patients prior to the development of clinically evident NAION. Boghen and Glaser[25] described one patient who at the time of presentation with NAION had optic disc edema in the asymptomatic contralateral eye, which subsequently developed visual field loss consistent with NAION 2 weeks later. Hayreh[66] reported 4 patients with bilateral NAION, all

of whom initially had visual loss in one eye and asymptomatic optic disc edema in the fellow eye. Each patient developed overt NAION in the second eye within weeks. Gordon and associates[67] reported 2 cases of asymptomatic optic disc edema with negative evaluation for specific etiology, both of which resolved spontaneously over 1 and 2 years. One patient was diabetic and one had previous NAION in the fellow eye. Prenner and associates[68] described a case of optic disc edema that persisted for 7 months until overt NAION developed. Fluorescein angiography was performed, but detailed early filling views were not included. Almog and Goldstein[69] reviewed a series of 23 cases of asymptomatic optic disc edema in vasculopathic patients (19 patients were diabetic). In 9 eyes, overt AION developed, within a mean interval of 16.8 weeks, whereas in 25 eyes, disc edema resolved over a mean of 15.5 weeks. The investigators postulated that the diabetic cases that resolved without developing overt NAION could be classified as "diabetic papillopathy." Hayreh and Zimmerman[70] recently reported on 54 patients, 60 involved eyes (from a cohort of 670 patients with NAION, and including the 4 patients described previously[66]), who presented with optic disc edema without optic nerve dysfunction. In 14 eyes (23.3%), there was progression to overt NAION over a median 5.8 weeks; in an additional 12 eyes (20%), NAION developed later, after resolution of the disc edema. In the remaining eyes, overt NAION did not occur during follow-up. In 30 patients (55%), the fellow eye had suffered NAION. On the basis of vasculopathic risk factors, lack of evidence for other cause of disc edema, evidence of AION in the fellow eye, and the later development in some patients of AION in the asymptomatically edematous eye, the disc edema in this scenario has been suggested to be ischemic in origin, including those that did not develop overt NAION (presumed reversible ischemia). In no case was impaired optic disc perfusion confirmed with early filling views on FA.

Diabetic Papillopathy

Initial descriptions of "diabetic papillopathy"[71-75] referred to a syndrome of unilateral or bilateral optic disc edema in young, type 1 diabetics, without evidence of increased intracranial pressure and without significant defects in visual field and pupillary function, which would be consistent with NAION or optic neuritis. Optic disc edema was prolonged in these cases, but vision generally was preserved. A later report by Regillo and associates[76] added a substantial number of older patients with type 2 diabetes. Overall, fewer than 100 total cases have been reported, and the specific criteria for diagnosis have been vague, especially regarding the allowable degree of optic nerve dysfunction and the corresponding differentiation from mild NAION.

The currently accepted criteria for the diagnosis of diabetic papillopathy include:

1. presence of diabetes (either type 1 or type 2);
2. optic disc edema (unilateral or bilateral);
3. absence of substantial optic nerve dysfunction (at most a minor afferent pupillary defect; minimal visual field defect, either enlarged blind spot or focal central depression if macular edema is present, specifically, no altitudinal visual field defect; visual acuity levels may vary, since coexisting maculopathy is a common confounding feature); and
4. lack of evidence for ocular inflammation or elevated intracranial pressure.

Patients typically present either with no visual complaints or with vague, nonspecific visual disturbance, such as mild blurring or distortion; transient visual obscurations have rarely been reported. Pain is absent, as are other ocular or neurologic symptoms.

The involved optic disc(s) may demonstrate either nonspecific hyperemic edema or marked dilation of the inner optic disc surface microvasculature (Figure 8). The surface vascular engorgement may be prominent enough in some cases to be mistaken for optic disc neovascularization (NVD). It may be distinguished from NVD by the radial pattern of vessels generally limited to the optic disc surface.

Occasionally, NVD may be superimposed on the edema of diabetic papillopathy (see "Diabetic Papillopathy" in the "Results" section).

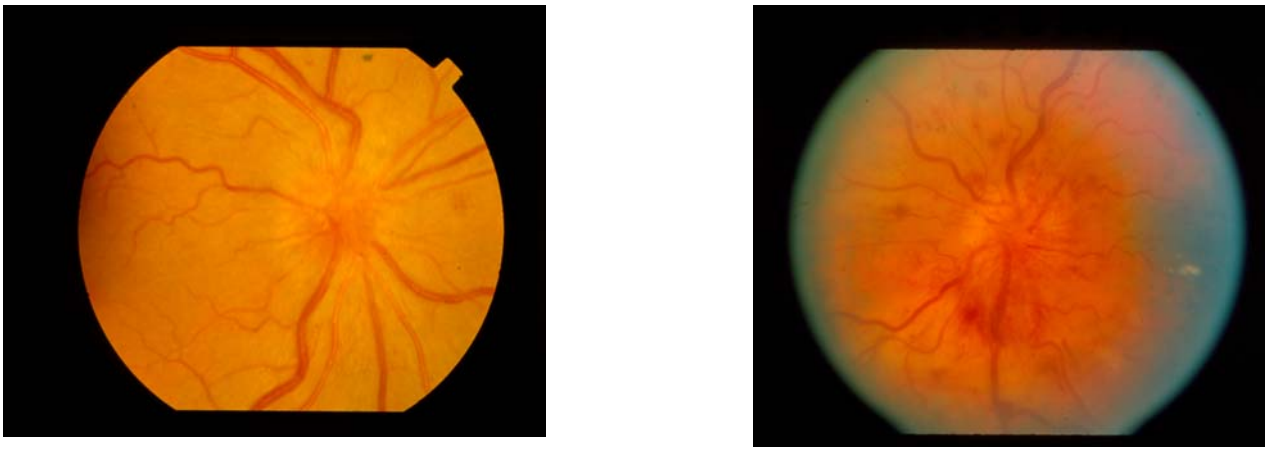

FIGURE 8

Fundus photograph showing diabetic papillopathy. Left, Optic disc with diffuse edema. Right, Optic disc with diffuse edema and prominent surface vascular dilation.

Diabetic papillopathy must also be distinguished from other causes of optic disc edema. Papilledema, optic disc edema secondary

to elevated intracranial pressure, is usually distinguished by symptoms of high intracranial pressure, but in cases with suspected bilateral diabetic papillopathy, neuroimaging and lumbar puncture may be required for differentiation. Disc edema related to systemic hypertension does not typically demonstrate prominent surface vascular engorgement and is usually associated with hypertensive retinopathy; blood pressure measurement is important in suspected cases. Papillitis and NAION both demonstrate significant optic nerve dysfunction, as evidenced by afferent pupillary defect and visual field loss.

The fellow eye frequently demonstrates a "crowded" optic disc with a small cup-disc ratio similar to the configuration seen in patients with NAION.[76] Optic disc edema may persist up to 12 months, after which it resolves spontaneously, leaving little or no optic atrophy.

The pathogenesis of diabetic papillopathy is unproven. Early investigators postulated either a toxic effect on the optic nerve secondary to abnormal glucose metabolism or an inner disc surface vascular disturbance, with resultant microvascular leakage into the optic disc.[72-75] Several investigators have postulated it to be a mild form of optic disc ischemia, which is reversible ischemia of both the prelaminar and inner surface layers of the optic nerve head.[67,75] The prominent surface telangiectasia seen in many cases is reminiscent of a similar phenomenon seen focally on the disc in NAION and may represent vascular shunting from prelaminar ischemic vascular beds.[77] The frequent occurrence of a "crowded" optic disc in the fellow eye, as in NAION, supports an ischemic mechanism as well. Hayreh and Zimmerman[78] have recently summarized a series of 206 diabetic patients with NAION, suggesting that patients with features consistent with the diabetic papillopathy syndrome are simply a part of the spectrum of NAION.

METHODS

The study was approved prospectively by the UCLA Office for Protection of Research Subjects Institutional Review Board for retrospective review of patient data (IRB G08-09-006-1, approval date September 26, 2008).

In order to identify the spectrum of clinical and fluorescein angiographic features of optic disc ischemia in patients younger than 50 years, we undertook a study that encompassed two phases:

1. Comparison of patients with NAION and onset under age 50 (NAIONy) to a cohort with NAION and onset at age 50 or older (NAIONo) with regard to vasculopathic risk factors, clinical features, and fluorescein angiographic features
2. Review of clinical and fluorescein angiographic features in patients under age 50 with pre-NAION optic disc edema and those with diabetic papillopathy

NAION IN YOUNG PATIENTS (NAIONy)

A computer search was performed of patients with the diagnosis of NAION seen at the Jules Stein Eye Institute, UCLA Department of Ophthalmology, Neuro-Ophthalmology Division, from 1986 through 2008, diagnosed according to our previously published criteria. Those with age at onset under 50 years were identified (NAIONy). A control group of patients aged 50 years or older with NAION diagnosed by the same criteria was randomly selected for comparison (NAIONo); patients with symptoms of giant cell arteritis, elevated erythrocyte sedimentation rate (age/2 for men, age + 10/2 for women), or simultaneous cilioretinal artery occlusion were excluded. All patients had undergone complete neuro-ophthalmologic evaluation, including dilated funduscopy and quantitative perimetry. No patients in either group demonstrated evidence of inflammatory optic neuropathy (optic neuritis), based on lack of pain on eye movement, other neurologic symptoms suggesting demyelination, substantial recovery of vision, or optic nerve enhancement on MRI. Patients with evidence of peri-NAION severe systemic hypotensive events were excluded.

The following clinical parameters were tabulated: initial and follow-up visual acuity and perimetry; optic disc cup-disc ratio (<0.2 considered structurally "crowded"); vasculopathic risk factors including systemic hypertension, diabetes, hyperlipidemia, smoking, CRF; ipsilateral recurrence of NAION (defined as another episode at least 2 months after stabilization of visual acuity and field and resolution of optic disc edema); progressive form of NAION (defined as worsening of visual acuity by at least 3 lines Snellen acuity or by at least 3.0 dB on quantitative perimetry during the first 30 days after initial visual loss); and fellow eye occurrence of NAION, including time to occurrence.

Statistical analysis was performed using SAS software version 9.2 (SAS, Inc, Cary, North Carolina). The differences in characteristics, such as gender, smoking, and comorbid conditions, between young and old NAION patients were compared using Fisher exact tests. The factors with $P<.2$ in the above comparisons were entered into a multivariable logistic regression model to estimate their effects on distinguishing between young and old NAION patients after controlling for potential confounding effects, and such effects were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The difference in the duration of follow-up was compared using the Wilcoxon rank sum test. The time to the onset of NAION in the fellow eye was estimated using a Kaplan-Meier survival analysis, and the difference in the time to the onset in the fellow eye between young and old NAION patients was compared using the log-rank test. The rate of fellow eye involvement and its 95% CI at specific time points was estimated from the Kaplan-Meier survival curve. The potential risk factors for the time to the onset of fellow eye were estimated separately for young and old NAION patients using Cox proportional hazard regression models. The risk factors with P<.2 in the univariate Cox proportional hazard regression models were entered into a multivariable Cox proportional hazard regression model to control for potential confounding effects. The effect of risk factors was expressed as hazard ratios (HRs) with 95% CI. In all analyses, $P<.05$ was considered as statistically significant.

Twenty-four patients underwent screening for hyperhomocysteinemia and prothrombotic risk factors (factor V Leiden, antithrombin III, protein C and S, anticardiolipin antibodies).

Fluorescein angiography was performed in 54 eyes by our previously reported technique for evaluating early optic disc filling characteristics. The following features were tabulated: delay of prelaminar optic disc filling by at least 5 seconds after choroidal

filling; superimposed segmental early optic disc hyperfluorescence; and peripapillary choroidal filling delay at least 5 seconds relative to remaining choroid.

DIABETIC PAPILLOPATHY

A second computer search was performed of patients seen in the Jules Stein Eye Institute, UCLA Department of Ophthalmology, Neuro-Ophthalmology Division, from 1986 through 2008 and coded as both diabetes and optic disc edema, but without the diagnosis of NAION. All patients had undergone complete neuro-ophthalmologic evaluation, including dilated funduscopy and quantitative perimetry, and all underwent FA by our previously reported technique for evaluating early optic disc filling characteristics. In cases with prominent optic disc surface vascular dilation, differentiation from NVD was based on the following characteristics (Figure 9):

1. Generally radial distribution of the dilated vessels in diabetic papillopathy, as opposed to the random branching pattern of NVD;
2. Limitation of the dilated vessels to the disc surface in diabetic papillopathy, as opposed to extension to surrounding retina or proliferation into the vitreous cavity with NVD; and
3. Limitation of fluorescein dye leakage to the disc substance and peripapillary retina in diabetic papillopathy, as opposed to extensive extrapapillary leakage and leakage anteriorly into the vitreous from NVD.

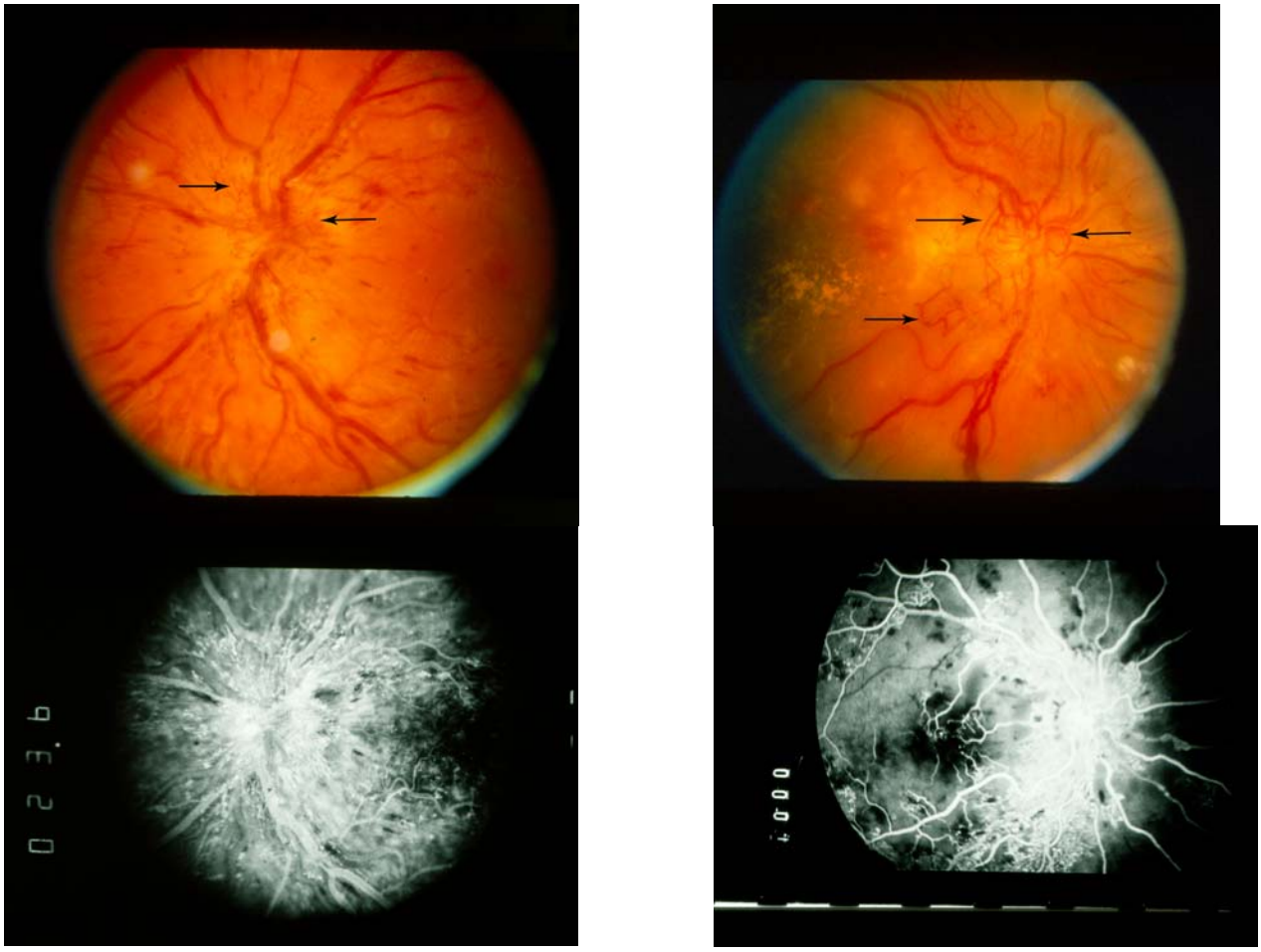

FIGURE 9

Fluorescein angiography, diabetic papillopathy vs optic disc neovascularization. Upper left, Diabetic papillopathy, fundus photograph, optic disc edema with prominent surface vascular dilation. Vessels (arrows) predominantly are radial and extend minimally past disc margin. Upper right, Diabetic papillopathy and optic disc neovascularization, fundus photograph, optic disc edema with optic disc neovascularization. Vessels (arrows) are nonradial, irregular, and extend far past disc margin. Lower left, Diabetic papillopathy, fluorescein angiogram, mid phase, optic disc edema with prominent surface vascular dilation; leakage is primarily from radial disc surface vessels extending adjacent to disc. Lower right, Diabetic papillopathy and optic disc neovascularization, fluorescein angiogram, mid phase, optic disc edema with optic disc neovascularization, leakage from disc is relatively mild compared with extensive irregular vascular abnormality and leakage throughout posterior pole.

All patients underwent MRI to rule out intracranial or optic nerve lesion. We included patients aged <50 years with the diagnosis of diabetic papillopathy based on the presence of either unilateral or bilateral optic disc edema without evidence of elevated intracranial pressure, ocular inflammation, or significant optic nerve dysfunction (more than trace afferent pupillary defect, visual field

defect other than enlarged blind spot, or focal central depression secondary to macular edema, features which would suggest overt NAION).

RESULTS

NAION IN YOUNG PATIENTS (NAIONy)

Of 848 patients with NAION, 108 (12.7%) under age 50 years (range 18-49, median 43) met criteria for study. Sixty-nine cases (8.1%) were 45 years or younger, 39 (4.6%) were 40 years or younger, and 18 (2.1%) were 35 years or younger. Fifty-six percent (61) were male. Magnetic resonance imaging of brain and orbits was performed in 88 of 108 (81.5%); no case showed evidence of optic nerve enhancement suggestive of optic neuritis.

Risk factors for NAIONy and NAIONo are compared in Table 1. Systemic hypertension was present in 35 of 108 patients (32.4%); diabetes mellitus was present in 15 of 107 (14.0%); CRF was present in 10 of 108 (9.3%); crowded discs (cup-disc ratio < 0.2) were present in 95 of 108 (87.9%); smoking history was present in 27 of 100 (27.0%); anemia was present in 8 of 86 (9.3%); migraine was present in 20 of 98 (20.4%); hyperlipidemia was present in 34 of 73 (46.6%). No patients showed hyperhomocysteinemia. Five patients demonstrated positive prothrombotic risk factors: one patient was positive for factor V Leiden and antithrombin III, one for anticardiolipin IgM antibodies, one for elevated protein S, one for elevated protein C and antithrombin III, and one for factor V Leiden mutation alone; all but the last case had bilateral involvement.

TABLE 1. COMPARISON OF RISK FACTORS BETWEEN PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONy) AND AGED 50 AND OVER (NAIONo)

RISK FACTOR	NAIONy N=108	NAIONo N=108	*P* VALUE*
Male gender	61 (56%)	61 (56%)	1.00
Hypertension	35 (32%)	55 (51%)	0.009
Diabetes	15 (14%); n=107	19 (18%); n=106	0.46
Chronic renal failure	10 (9%)	2 (2%)	0.033
Crowded disc	95 (88%)	85 (79%); n=107	0.099
Smoking	27 (27%); n=100	21 (23%); n=90	0.62
Anemia	8 (9%); n=86	3 (6%); n=54	0.53
Migraine	20 (20%); n=98	9 (9%); n=102	0.026
Hyperlipidemia	34 (47%); n=73	36 (63%); n=57	0.077

*Fisher exact test.

As seen in Table 2, four factors reached statistical significance: systemic hypertension was less common in NAIONy (35/108, 32.4 % vs 55/108, 50.9 %, $P = .009$, Fisher exact test; using the multivariable logistic regression model, OR = 0.44, $P = .008$); CRF with dialysis was more common in NAIONy (10/108, 9.3 % vs 2/108, 1.9 %, $P = .033$, Fisher exact test; using the multivariable logistic regression model, OR = 13.50, $P = .002$), as was migraine (20/98, 20.4% vs 9/102, 8.8%, $P = .026$, Fisher exact test; using the multivariable logistic regression model, OR = 2.45, $P = .043$). Crowded discs were more common in NAIONy when analyzed using the multivariable logistic regression model (OR = 2.78, $P = .025$)

TABLE 2. ADJUSTED EFFECT OF RISK FACTORS FOR PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONy) FROM MULTIVARIABLE LOGISTIC REGRESSION MODEL (N = 200)

RISK FACTOR*	ODDS RATIO	95% CONFIDENCE INTERVAL	*P* VALUE
Hypertension	0.44	0.24 - 0.81	.008
Chronic renal failure	13.50	2.51 - 72.48	.002
Crowded disc	2.78	1.14 - 6.75	.025
Migraine	2.45	1.03 - 5.85	.043

*Risk factors with $P<.2$ in the unadjusted comparisons were entered into the multivariable logistic regression model.

Comparison of fellow eye involvement in NAIONy and NAIONo is shown in Table 3. Bilateral involvement occurred in 46 (42.6%) of 108 patients with NAIONy, compared to 32 (29.6%) of 108 patients with NAIONo (chi-square test, $P = .047$), a statistically significant difference. Of NAIONy patients with bilateral involvement, one had bilateral simultaneous occurrence, 2 had prior documented NAION, and 43 of 108 (39.8 %) had documented sequential events, with median time between episodes 12 months, mean 28.9 (range, 1-216). All 32 bilateral cases of NAIONo were documented sequential events, with median time between episodes

7.5 months, mean 22.8, range 1-196). Median overall follow-up for NAIONy patients was 6 months (mean 23.9, range 1-224) and also 6 months (mean 17.5, range 1-196) for the NAIONo group. Kaplan-Meier analysis is illustrated in Table 3 and Figure 10. A statistically significant difference between the curves overall was not detected (log-rank test, *P* = .49), although a trend toward separation does begin at 1 year, with the 12-month Kaplan-Meier estimate 41% for NAIONy vs 30% for NAIONo.

TABLE 3. COMPARISON OF FOLLOW-UP AND FELLOW EYE INVOLVEMENT BETWEEN PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONy) AND AGED 50 AND OVER (NAIONo)

VARIABLE	NAIONy N=108	NAIONo N=108	*P* VALUE
Duration of follow-up (months)			.52*
Mean±SD	23.9 ± 41.0	17.5 ± 29.8	
Median (range)	6 (1 - 224)	6 (1 - 196)	
Fellow eye involvement			
All	46 (43%)	32 (30%)	.047†
6-month KM estimate	19% (95% CI: 12% - 29%)	19% (95% CI: 11% - 30%)	
12-month KM estimate	41% (95% CI: 29% - 54%)	33% (95% CI: 22% - 47%)	

KM, Kaplan-Meier.
*Wilcoxon rank sum test.
†Chi-square test (log-rank test *P*=.31 for the time to second eye involvement).

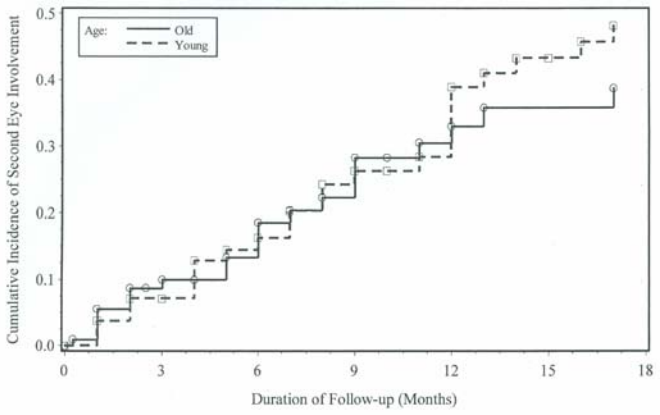

FIGURE 10

Kaplan-Meier curve of time to fellow eye involvement (up to 18 months) among 213 nonarteritic anterior ischemic optic neuropathy (NAION) patients without bilateral involvement at onset. Log-rank test *P* = .49 for comparing Kaplan-Meier curves between patients with NAION under age 50 (NAIONy, 43 of 105 patients [41%] with fellow eye involvement) and patients with NAION aged 50 and over (NAIONo, 32 of 108 patients [30%] with fellow eye involvement).

Risk factors for fellow eye involvement are summarized in Tables 4 and 5. Diabetes (HR = 4.54, *P* = .001, multivariable Cox proportional hazards regression model) and CRF (HR = 3.87, *P* = .018, multivariable Cox proportional hazards regression model) showed statistically significant risk for fellow eye involvement in NAIONy, whereas CRF also was a significant risk for fellow eye involvement in NAIONo (HR = 19.54, *P* = .008, multivariable Cox proportional hazards regression model).

Initial and follow-up levels of visual acuity and visual field sensitivity were not statistically significantly different between the NAIONy and NAIONo groups. The progressive form occurred in 44 (40.7%) of 108 patients and 52 (33.8%) of 154 eyes in NAIONy, compared with 55 (50.9%) of 108 and 67 (47.9%) of 140 eyes in NAIONo (*P* = .13, Fisher exact test). Recurrence developed in 5 (4.6%) of 108 patients and 5 (3.2%) of 154 eyes with NAIONy, compared with 3 (2.8%) of 108 patients and 3 (2.1%) of 140 eyes with NAIONo (*P* = .73, Fisher exact test). Neither of these features was significantly different between groups.

Forty-four of 54 eyes (81.5%) with FA demonstrated segmental or diffuse optic disc filling delay of ≥5 seconds after choroidal filling, confirming an ischemic pattern (Figure 11). Segmental early hyperfluorescence was present in 26 of 54 (48.1%) (Figure 12). Peripapillary choroidal filling delay was seen in 12 of 54 (22.2%). The optic disc filling characteristics of these and the other optic disc ischemic syndromes studied here are summarized in Table 6.

Chronic Renal Failure With Dialysis

Of NAIONy patients, 10 were on dialysis for CRF; seven were under age 40 (mean 36.5 years, median 37.5, range 18-47). Demographic features are listed in Table 7. Six were bilateral, 2 of these with simultaneous onset, for a total of 16 eyes. Visual loss was severe (light perception or no light perception) in 3 (18.8%) of 16 eyes. Crowded optic disc (cup-disc ratio <0.2) was present in only 12 (60.0%) of 20 eyes. Anemia was present in all 10 patients and history of hypertension in 6. Diabetes was present in only one.

Fluorescein angiography was performed in 6 cases; all demonstrated delayed optic disc filling consistent with ischemia. Two of 6 showed segmental early hyperfluorescence, and 2 showed peripapillary choroidal filling delay. Marked pallor and filling delay were characteristic of this group (Figure 13).

TABLE 4. UNADJUSTED EFFECT OF RISK FACTORS FOR FELLOW EYE INVOLVEMENT FROM UNIVARIATE COX PROPORTIONAL HAZARDS REGRESION MODELS STRATIFIED BY AGE BETWEEN PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONY) AND AGED 50 AND OVER (NAIONO)

RISK FACTOR	NAIONy N=108	NAIONo N=108
Male gender	HR=0.58 95% CI=0.31 - 1.07 *P*=.080	HR=0.67 95% CI=0.31 - 1.42 *P*=.29
Hypertension	HR=0.66 95% CI=0.35 - 1.23 *P*=.19	HR=1.25 95% CI=0.61 - 2.55 *P*=.54
Diabetes	HR=3.10 95% CI=1.49 - 6.46 *P*=.003 n=107	HR=1.03 95% CI=0.42 - 2.53 *P*=.95 n=106
Chronic renal failure	HR=2.34 95% CI=0.98 - 5.60 *P*=.057	HR=5.50 95% CI=0.71 - 42.71 *P*=.10
Crowded disc	HR=1.26 95% CI=0.45 - 3.55 *P*=.66	HR=2.65 95% CI=0.92 - 7.68 *P*=.072 n=107
Anemia	HR=1.64 95% CI=0.57 - 4.72 *P*=.36 n=86	HR=1.50 95% CI=0.19 - 11.63 *P*=.70 n=54
Migraine	HR=1.75 95% CI=0.88 - 3.46 *P*=.11 n=98	HR=1.03 95% CI=0.31 - 3.45 *P*=.96 n=102
Hyperlipidemia	HR=1.03 95% CI=0.48 - 2.22 *P*=.94 n=73	HR=1.88 95% CI=0.58 - 6.08 *P*=.29 n=57
Smoking	HR=0.49 95% CI=0.23 - 1.02 *P*=.058 n=100	HR=1.82 95% CI=0.75-4.44 *P*=.19 n=90

CI, confidence interval; HR, hazard ratio.

Pre-NAION Ischemic Edema

In one case, FA was performed during a period of optic disc edema prior to visual field loss. The patient was 43 years old when he originally suffered NAION in his right eye. Vision remained stable for 9 years until he developed photopsia in the left eye, and on evaluation 2 weeks later, examination revealed visual acuity of 20 of 15 in the left eye, with normal pupillary light reaction and quantitative perimetry; the right eye demonstrated an inferior altitudinal visual field defect from prior NAION (Figure 14). The left optic disc was edematous, with a single flame hemorrhage adjacent (Figure 14). The right optic disc was atrophic after the previous NAION (Figure 15). Fluorescein angiography revealed left optic disc filling delay with segmental early hyperfluorescence temporally (Figure 15) consistent with the segmental pattern of ischemia previously seen in NAION (Figure 6). Peripapillary choroidal filling delay was not seen. Two weeks later, he developed an inferior altitudinal visual field defect typical for NAION (Figure 14), which has remained stable as the optic disc edema resolved.

DIABETIC PAPILLOPATHY

Thirty-two patients met the criteria for diagnosis of diabetic papillopathy. Of these, 12 (37.5 %) were under age 50 (mean 42.2 years, median 47, range 16-49). Demographic features are listed in Table 8. Two were bilateral at onset, for a total of 14 eyes. Duration of follow-up ranged from 2 to 120 months (median 6, mean 19.6). Aside from diabetes, vasculopathic risk factors were identified in 5 (41.7%) of 12 patients.

TABLE 5. ADJUSTED EFFECT OF RISK FACTORS FOR FELLOW EYE INVOLVEMENT FROM MULTIVARIABLE COX PROPORTIONAL HAZARDS REGRESION MODELS STRATIFIED BY AGE BETWEEN PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONy) AND AGED 50 AND OVER (NAIONo)

RISK FACTOR*	NAIONy N=92	NAIONo N=90
Male gender	HR=0.66 95% CI=0.30 - 1.46 *P*=.31	…
Hypertension	HR=0.64 95% CI=0.31 - 1.33 *P*=.23	…
Diabetes	HR=4.54 95% CI=1.84 - 11.22 *P*=.001	…
Chronic renal failure	HR=3.87 95% CI=1.26 - 11.86 *P*=.018	HR=19.54 95% CI=2.21 - 172.50 *P*=.008
Crowded disc		HR=2.99 95% CI=0.85 - 10.48 *P*=.087
Smoking	HR=0.68 95% CI=0.28 - 1.62 *P*=.38	HR=2.18 95% CI=0.88 - 5.41 *P*=.093
Migraine	HR=1.81 95% CI=0.79 - 4.18 *P*=.17	…

CI, confidence interval; HR, hazard ratio.
*Risk factors with *P*<.2 in the unadjusted analyses were entered into the multivariable Cox proportional hazards regression model.

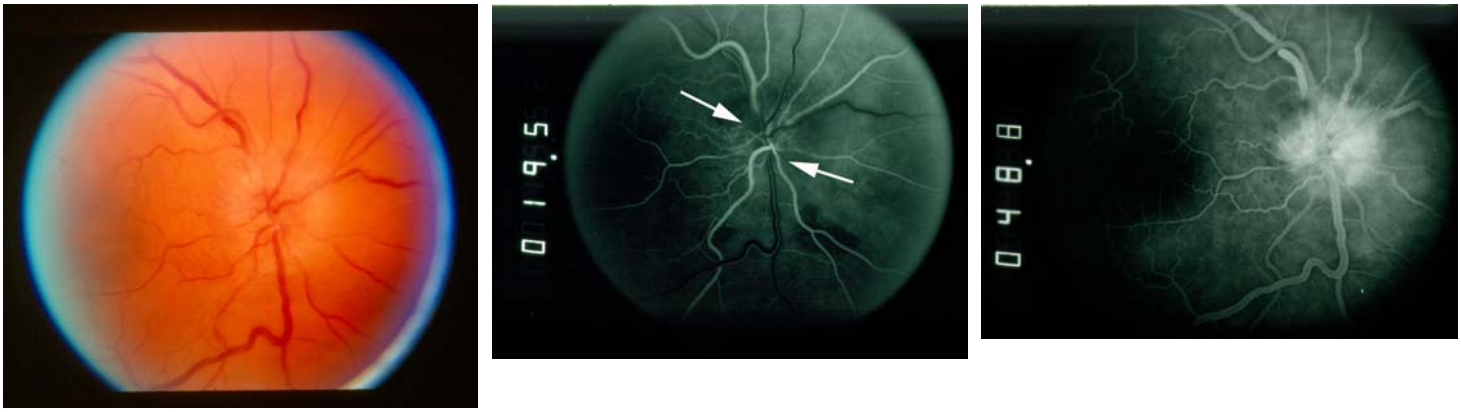

FIGURE 11

Fluorescein angiography in nonarteritic anterior ischemic optic neuropathy in young patients (NAIONy) diffuse. Left, Fundus photograph showing diffuse optic disc edema. Middle, Fluorescein angiogram, early arteriovenous phase, showing poor filling of optic disc (arrows) at 19.5 seconds. Right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 48.8 seconds.

Visual acuity ranged from 20/20 to 20/80 at presentation. Blind spot enlargement was the only visual field defect in 10 (71.4%) of 14 eyes, with 2 (14.3%) of 14 demonstrating blind spot enlargement plus very subtle central depression secondary to cystoid macular edema. Two of 14 eyes (14.3%) showed normal visual fields. Crowded disc (cup-disc ratio <0.2) was present in all eyes. Disc edema showed prominent surface vascular dilation (Figure 14) in 9 (64.3%) of 14 eyes, with the remainder showing diffuse, nonspecific edema (Figure 16). Proliferative diabetic retinopathy (PDR) was present in 3 eyes (21.4%); nonproliferative diabetic retinopathy (NPDR) was seen in 9 eyes (64.3%), with clinical cystoid macular edemah seen in 3 eyes (21.4%). Optic disc edema resolution was documented from 2 to 12 months (median 5, mean 5.3). Optic atrophy (trace - 1+ maximum) was present in 6 eyes (42.9%) at

resolution of optic disc edema; the remainder showed normal appearance (Figure 16). Two cases (16.7%) had previously documented NAION in the fellow eye. In one case (8.3%), NAION developed in the affected eye 2 years after resolution of optic disc edema.

Fluorescein angiography was performed in 10 (71.4%) of 14 eyes. Seven of 10 (70.0%) demonstrated delayed optic disc filling consistent with ischemia. In cases with optic disc edema and prominent surface vascular dilation, early filling was delayed as in NAION, and subsequent early leakage from the dilated vessels was noted (Figure 17). In cases with nonspecific optic disc edema, early filling was delayed as in NAION. In 4 cases (40.0%), the segmental filling pattern seen in NAION was noted (Figure 18). Peripapillary choroidal filling delay was present in 2 (20.0%).

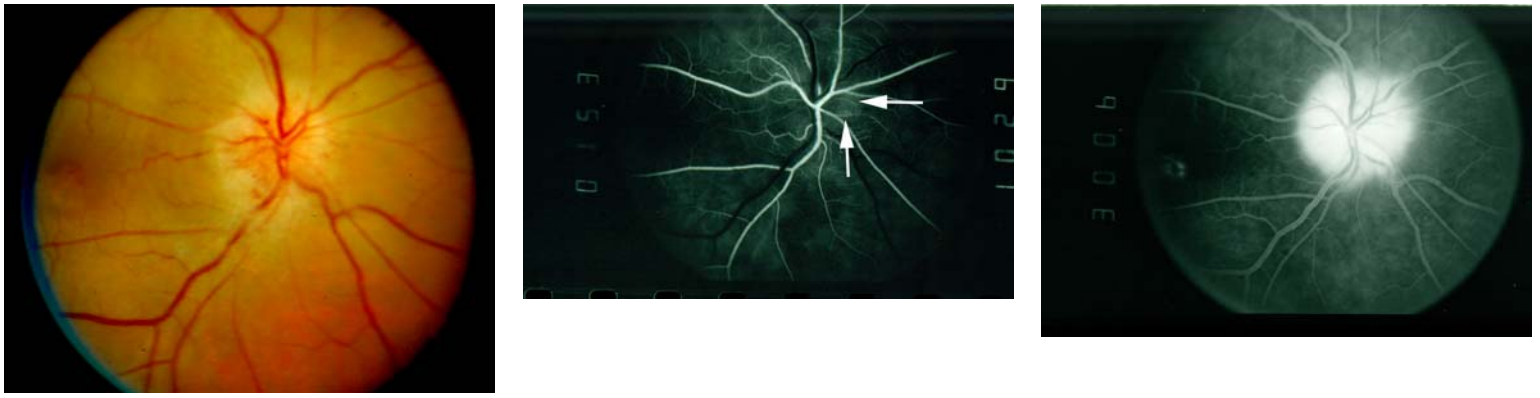

FIGURE 12

Fluorescein angiography in nonarteritic anterior ischemic optic neuropathy in young patients (NAIONy) segmental. Left, Fundus photograph showing diffuse optic disc edema. Middle, Fluorescein angiogram, early arteriovenous phase, showing poor filling of optic disc with relatively spared segmental region of early filling (arrows) at 15.3 seconds. Right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 300.6 seconds.

TABLE 6. FLUORESCEIN ANGIOGRAPHIC OPTIC DISC FILLING CHARACTERISTICS IN OPTIC DISC ISCHEMIC SYNDROMES

SYNDROME	OPTIC DISC FILLING DELAY	OPTIC DISC SEGMENTAL FILLING	CHOROIDAL FILLING DELAY
NAIONo	31/41 (75.6%)	22/41 (53.7%)	11/41 (26.8%)
NAIONy	44/54 (81.5%)	26/54 (48.1%)	12/54 (22.2%)
CRF	6/6	2/6	2/6
DP	7/10 (70.0%)	4/10 (40.0%)	2/10 (20.0%)
PRE-NAION	1/1	1/1	0/1

CRF, chronic renal failure; DP, diabetic papillopathy; NAIONo, nonarteritic anterior ischemic optic neuropathy in patients aged ≥50; NAIONy, nonarteritic anterior ischemic optic neuropathy in patients aged <50; PRE-NAION, optic disc edema pre-onset of NAION.

TABLE 7. SUMMARY OF CLINICAL CHARACTERISTICS OF PATIENTS WITH NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY UNDER AGE 50 (NAIONY) WITH CHRONIC RENAL FAILURE WITH DIALYSIS

PATIENT	AGE	GENDER	EYE	MIGRAINE	ANEMIA	DIABETES	HYPER-TENSION	HYPER-LIPIDEMIA	SMOKER	ACUITY	CUP-DISC RATIO	PROGRESSION	RECURRENCE	SECOND EYE (MONTHS)	FOLLOW-UP (MONTHS)
1	47	M	OD	-	+	+	+	+	-	20/25	0.5	-	-		
			OS							20/30	0.4	+ 8	-	+ 60	62
2	28	F	OD	-	+	-	-	-	-	CF	0.1		-	-	
			OS							CF	0.1	+ 6	-	+ (3)	26
3	18	F	OU	-	+	-	-	-	-	LP	0.0	-	-		
										20/200	0.0	-	-	0	2
4	33	F	OS	-	+	-	+	-	-	20/20	0.2	+ 7	-	-	3
5	47	M	OU	-	+	-	+	-	-	20/25	0.0	-	-		
										20/70	0.0	+ 6	-	0	1
6	37	F	OS	-	+	-	+	-	-	20/100	0.1	-	+	-	120
7	39	M	OD	-	+	-	-	-	+	NLP	0.3	-	-	-	4
8	36	F	OS	-	+	-	-	-	-	20/20	0.3	-	-	-	
			OD							20/25	0.3	-	-	+ 8	40
9	38	F	OD	-	+	-	+	-	-	NLP	0.5	+ 5	-		
			OS							20/25	0.5			+ 19	36
10	42	M	OS	-	+	-	+	+	-	20/30	0.1	-	-	-	2

CF, counting fingers; LP, light perception; NLP, no light perception; OD, right eye; OS, left eye; +, present; -, absent.

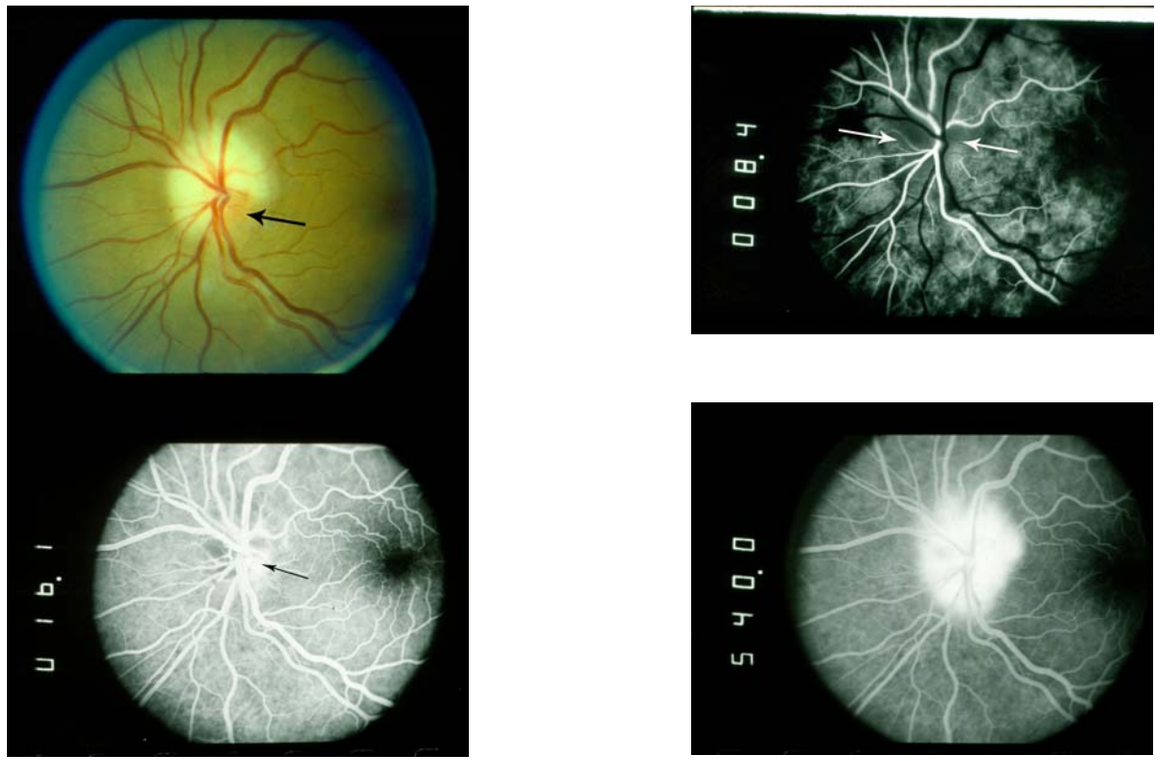

FIGURE 13

Fluorescein angiography in nonarteritic anterior ischemic optic neuropathy in young patients (NAIONy), chronic renal failure (CRF). Upper left, Fundus photograph showing segmental, pale optic disc edema. Inferotemporal segment (arrow) is relatively spared. Upper right, Fluorescein angiogram, early arteriovenous phase, showing diffusely poor filling of the optic disc (arrows) at 8.4 seconds. Lower left, Fluorescein angiogram, early arteriovenous phase, showing diffusely poor filling of the optic disc with inferotemporal segment of relatively intact filling (arrow) at 16.1 seconds. Lower right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 540.0 seconds.

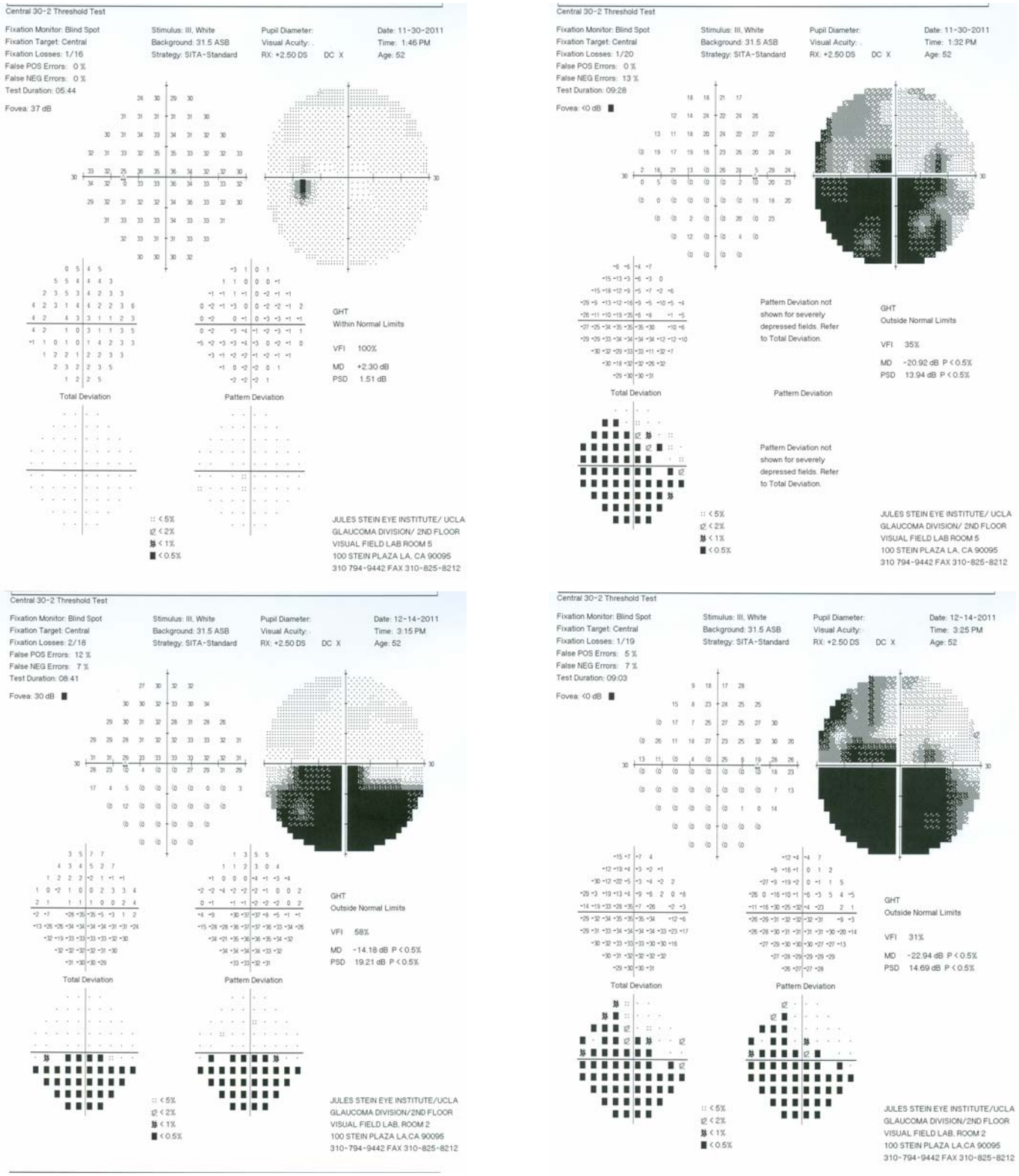

FIGURE 14

Visual fields in pre-nonarteritic anterior ischemic optic neuropathy optic disc edema. Upper left, Quantitative perimetry showing normal visual field, left eye. Upper right, Quantitative perimetry showing inferior altitudinal visual field defect, right eye. Lower left, Quantitative perimetry showing inferior altitudinal visual field defect, left eye. Lower right, Quantitative perimetry showing inferior altitudinal visual field defect, right eye.

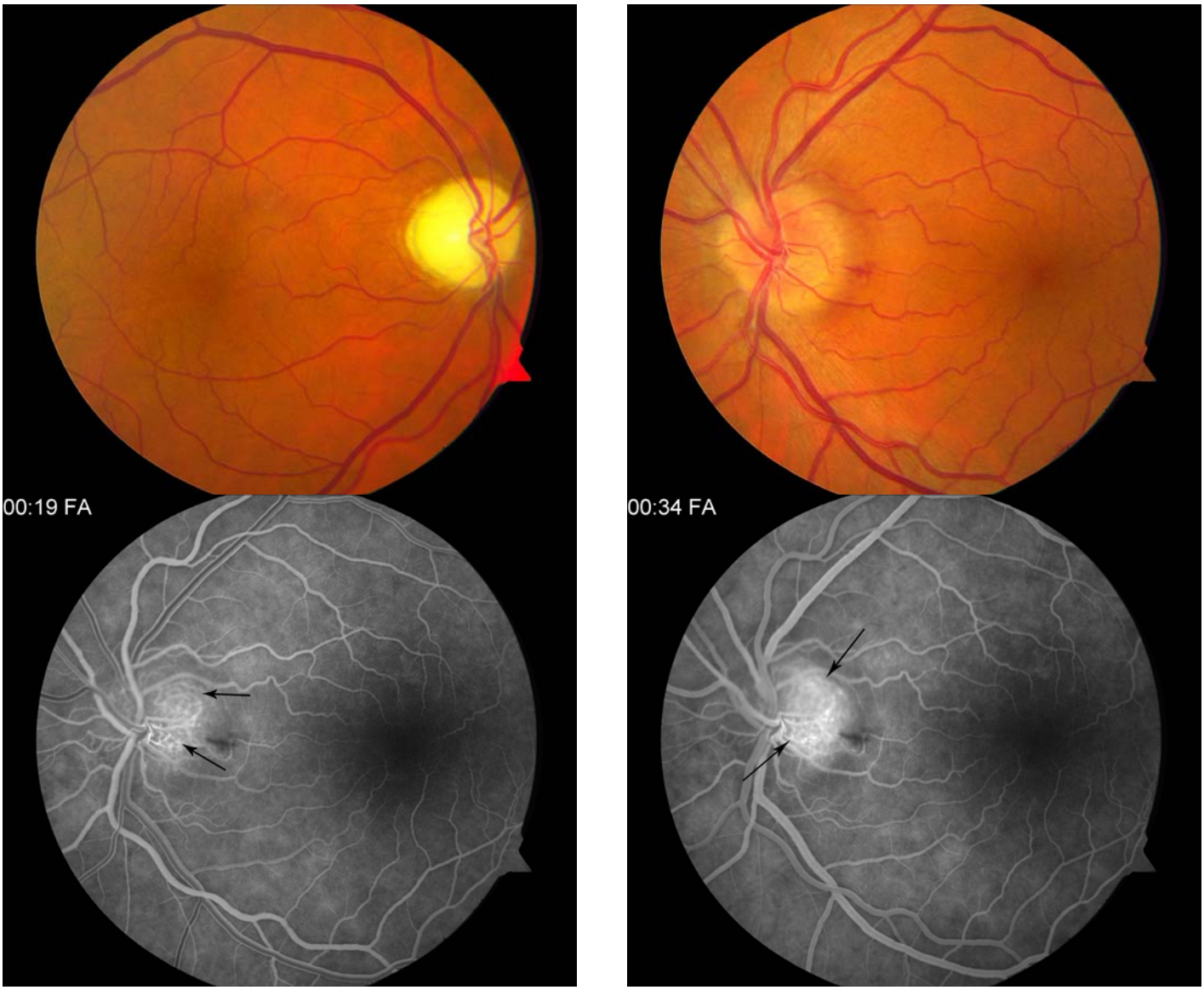

FIGURE 15

Fluorescein angiography in pre-nonarteritic anterior ischemic optic neuropathy optic disc edema. Upper left, Fundus photograph, right eye, showing optic atrophy from prior NAION. Upper right, Fundus photograph, left eye, showing diffuse optic disc edema. Lower left, Fluorescein angiogram, arteriovenous phase, showing poor filling of optic disc with relatively spared segment temporally (arrows) at 19.0 seconds. Fluorescein angiogram, mid phase, showing continued poor filling of optic disc with progressive hyperfluorescence at relatively spared segment temporally (arrows) at 34.0 seconds.

TABLE 8. SUMMARY OF CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC PAPILLOPATHY

PATIENT	AGE	GENDER	EYE	TYPE	DIABETES DURATION (MONTHS)	HYPER-TENSION	HYPER-LIPIDEMIA	SMOKER	ACUITY	VISUAL FIELD	CUP-DISC RATIO	DISC VASCULAR DILATION	DIABETIC RETINO-PATHY	RESO-LUTION (MONTHS)	OPTIC ATROPHY	FOLLOW-UP (MONTHS)
1	49	F	OD	2	48	-	-	-	20/20	NL	0.1	-	-	3	1+	3
2	46	F	OD	1	12	+	X	X	20/80	BS	0.1	+	PDR	5	-	5
3	16	F	OU	1	168	-	-	-	20/25,	CS	0.0 0.0	+	NPDR,CME,	5	-	6
									20/80			+	NPDR	5	-	6
4	48	M	OD	2	240	+	+	+	20/40	CS	0.0	+	NPDR,CME	3	1+	2
5	33	M	OD	1	260	-	-	X	20/80	BS	0.0	-	PDR,CME	2	1+	120
6	47	F	OD	1	492	-	-	+	20/20	BS	0.0	-	PDR	3	-	5
7	44	F	OS	1	300	-	-	-	20/40	BS	0.1	+	NPDR	4	TR	32
8	49	M	OD	2	120	-	-	-	20/40	BS	0.1	-	NPDR	12	TR	33
9	49	M	OS	2	84	-	+	+	20/50	BS	0.1	+	NPDR	12	1+	12
10	28	F	OS	1	180	-	-	-	20/20	BS	0.0	+	NPDR	2	-	4
11	48	F	OU	2	84	+	+	-	20/25	BS	0.1	+	NPDR	6	-	7
									20/25	BS	0.0	+	NPDR	6	-	7
12	49	F	OD	2	48	-	-	-	20/20	NL	0.1	-	-	6	-	6

BS, blind spot enlargement; CME, cystoid macular edema; CS, cecocentral;, NL, normal; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; X, data not available.

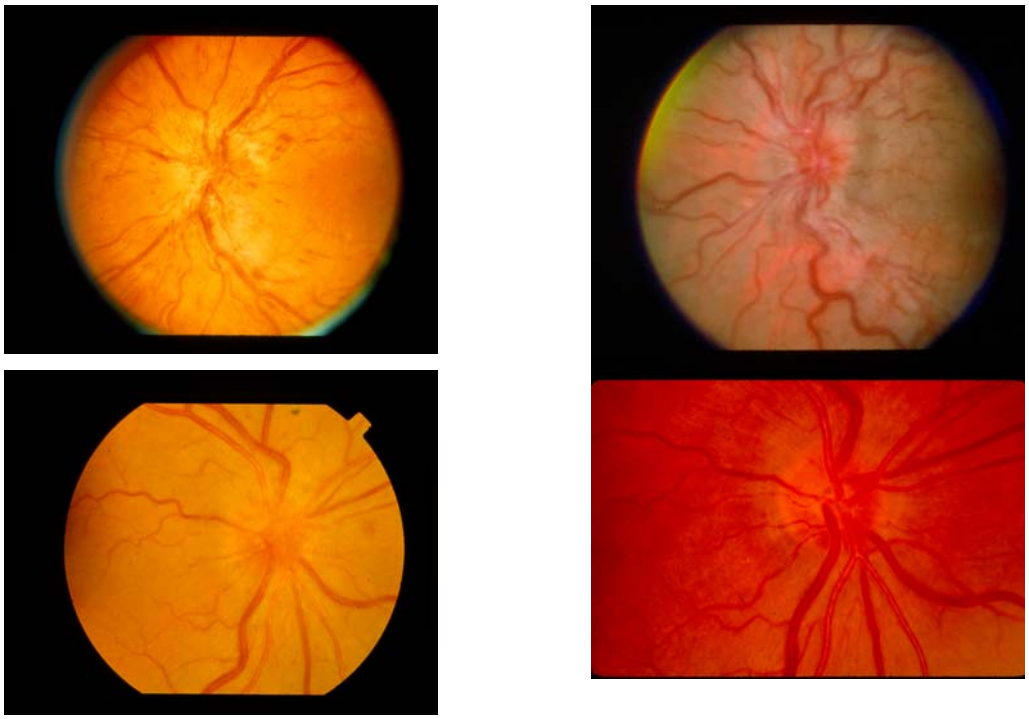

FIGURE 16

Fundus photograph in diabetic papillopathy. Upper left, Optic disc left eye with diffuse edema and prominent surface vascular dilation. Upper right, Optic disc left eye with diffuse nonspecific edema. Lower left, Optic disc right eye with diffuse nonspecific edema at initial presentation. Lower right, Optic disc right eye after resolution of edema (3 months), showing normal appearance.

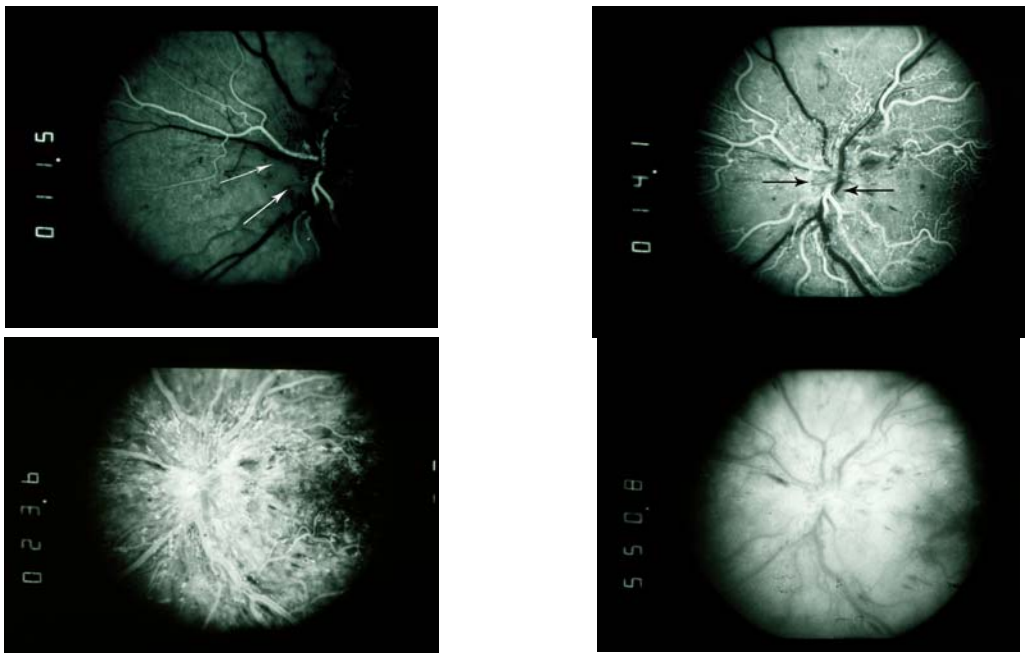

FIGURE 17

Fluorescein angiography in diabetic papillopathy with prominent surface vascular dilation. Upper left, Fluorescein angiogram, early arteriovenous phase, showing absent optic disc filling (arrows) at 11.5 seconds. Upper right, Fluorescein angiogram, early arteriovenous phase, showing poor optic disc filling (arrows) and very early leakage from adjacent surface vessels at 14.1 seconds. Lower left, Fluorescein angiogram, mid phase, showing diffuse early leakage from dilated surface vessels at 23.6 seconds. Prelaminar layer of disc filling is obscured by dilated leaking surface vasculature. Lower right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 550.8 seconds.

FIGURE 18

Fluorescein angiography in diabetic papillopathy with nonspecific diffuse edema. Left, Fluorescein angiogram, early arteriovenous phase, showing nearly absent filling of the optic disc with temporal segment of relatively intact filling (arrow) at 11.3 seconds. Middle, Fluorescein angiogram, early arteriovenous phase, showing poor filling of the optic disc nasally (long arrows), with temporal segment of progressive hyperfluorescence at relatively spared segment temporally (short arrows) at 13.0 seconds. Right, Fluorescein angiogram, late phase, showing late leakage from optic disc at 263.9 seconds.

DISCUSSION

NAION IN YOUNG PATIENTS (NAIONy)

Certain of the early case series of NAION included patients with onset under age 50; these were generally felt to be rare, although Guyer and associates'[27] original paper included 21 (10.5%) under age 50. Analyses of the frequency of NAION in this age-group probably underestimated it because of this bias, classifying many cases of acute optic neuropathy in younger patients as optic neuritis. The IONDT, as well as other more recent series of NAION patients, excluded those under age 50 to avoid misdiagnosis. Conversely, in any study of younger patients with NAION, it is essential to rule out optic nerve inflammation, either idiopathic demyelination or other causes, such as vasculitis or infection, in addition to other entities that might masquerade as ischemia, such as infiltration or compression. Rizzo and Lessell[79] outlined clinical criteria by which to differentiate optic neuritis from ischemia. Additionally, neuroimaging usually is sufficient to rule out involvement of the retrobulbar portion of the optic nerve by other processes.[80] In earlier series, it is difficult to ascertain which of these criteria were utilized to rule out these other potential entities. Recent studies of NAION in young patients[35,55] used these clinical criteria for diagnosis, finding from 7.5% to 23.2% of their NAION cases had onset under age 50. Variation in the frequency of NAIONy may reflect referral bias for these consultative practices. Our data confirm that NAION is not uncommon in patients under age 50, occurring in 12.7% of our cohort of patients. Fluorescein angiography focused on the early filling of the optic disc to document delay provides an accurate measure to confirm ischemia. Our study is the only one to utilize this feature in conjunction with other criteria to provide confirmatory evidence that our cases were indeed NAION, finding 81.5% of 54 eyes demonstrating filling delay, consistent with the previously reported rate of 76 % in NAION over age 50.

We attempted to clarify whether commonly proposed vasculopathic risk factors were more frequent in the NAIONy group and thus predisposed to earlier onset of the ischemic event. As noted in the "Introduction," previous studies of NAION (in all age-groups) have assessed the role of these factors when compared to either prior population studies or to current control groups; diabetes was the single factor that was consistently identified in all age-groups, and it also was associated with a younger age at onset in the overall NAION population. The two prior series of NAIONy patients addressed the issue in different ways. The study of Deramo and associates[35] compared patient data to a control group of non-NAION patients age- and gender-matched to the study group, finding that hypercholesterolemia (9/37, 24.3% vs 7/74, 9.5%, P = .036 chi-square) and diabetes (5/37, 13.5% vs 2/74, 2.7%, P = .027, chi-square) were both significantly more frequent in NAIONy, but hypertension and smoking were not. In the study of Preechawat and associates,[55] diabetes was present in 35 of 169 (20.7%), hyperlipidemia in 39 of 169 (23.0%), smoking in 49 of 169 (29.0%), anemia in 11 of 169 (6.5%), and hypertension in 59 of 169 (34.9%). These data were compared to other series of NAION in all age-groups, with similar values for all except CRF, which was present in 8 of 169 (4.7%), compared with 1% to 2% in very limited data for other series; however, no direct statistical comparisons were made.

Ours is the only study to date that compared a cohort of NAIONy patients directly to a cohort of NAIONo patients with regard to risk factors. As may be seen from Tables 1 and 2, NAIONy was statistically significantly more frequently associated with CRF, migraine, and crowded discs, but not with diabetes or hyperlipidemia. While the frequency of occurrence of both diabetes (15/107, 14.0%) and hyperlipidemia (34/73, 46.6%) was in keeping with other series, it was not significantly increased over our NAIONo group. The association with CRF was highly significant; this subgroup is described in detail below. The association of migraine with NAIONy has not been addressed in other studies; it raises the issue of vasospasm in the pathogenesis of NAION and whether this may be more substantial in young patients. It has also been implicated as a possible pathogenetic mechanism in glaucoma.[81] Case reports

have implicated beta-blockers used for migraine prophylaxis as a potential causative factor in the development of NAION.[82] We did not assess the relation of beta-blocker use to NAION event in this series. The NAIONo group demonstrated unusually high rates of both hypertension (55/108, 50.9%) and hyperlipidemia (36/57, 63.2%). Although this control group was relatively large and randomly selected, we suspect that this represents sample bias related to a highly selected group of more severe vasculopathic patients with NAION. This might also explain the mildly lower rate of crowded discs than expected from other studies (85/107, 79.4%); we typically consider more severe vasculopathy to be more frequently associated with AION in noncrowded optic discs. This is the case in arteritic AION, in which severe AION occurs without crowded discs,[83] and it also may play a role in patients with CRF, who showed a lower rate of crowded discs (9/16, 56.3%) in our series.

While our study was not designed to compare prothrombotic risk factors between groups, we did test 24 NAIONy patients for these abnormalities, finding 5 cases (20.8%) with abnormalities as noted above; four of these had bilateral optic neuropathy. Preechawat and associates[55] found 9 cases positive in their NAIONy series. These data suggest that screening in patients under age 50 is worthwhile, especially as treatment may be of value in reducing risk of fellow eye involvement.

Because early reports[48-52] suggested that NAION in young patients had a higher rate of ipsilateral eye recurrence than that in older patients, as reported by Repka and associates[26] (3.6%) and Hayreh and associates[41] (6.4%), we compared recurrence rates between NAIONy and NAIONo groups. In our series, the number of cases with recurrence was small, with 5 (3.2%) of 154 eyes with NAIONy documented, compared with 3 (2.1%) of 140 eyes with NAIONo (P = .73, Fisher exact test). Preechawat and associates[55] reported 11 eyes of 10 patients (5.9%) with recurrent episodes. Neither of our series confirms a significantly higher rate of recurrence in NAIONy.

We also assessed whether NAIONy patients had a more aggressive form of NAION based on a progressive deterioration profile. Progressive NAION, in which visual loss worsens either in episodes or steadily after initial loss, followed by stabilization at 6 to 8 weeks, has been suggested to be more frequent in young patients, although no series addresses this aspect specifically. The phenomenon has been reported in the range of 22% to 37%[25,50,84,85] for NAION overall. The progressive form occurred in our series in 44 (40.7%) of 108 patients and 52 (33.8%) of 154 eyes in NAIONy, compared with 55 of 108 (50.9%) and 67 (47.9%) of 140 eyes in NAIONo (P = .13, Fisher exact test). While there was no significant difference between groups, the values for each group were higher than literature reports. This may again reflect referral bias of more aggressive cases to our consultative practice. Alternatively, the figures may reflect initial evaluation of our patients earlier in the course of the disease, allowing for documentation of a greater number of patients with progressive visual loss prior to stabilization at 6 to 8 weeks.

The rate of fellow eye involvement in NAION without regard to age has been controversial. Estimates of bilaterality with varying follow-up have ranged from 24% to 39%.[26,42-45] Two major series, as noted above,[46,47] reported bilaterality figures of 30.6% and 31.4% at median follow-up of 5 years; the estimated fellow eye involvement rate for NAION at 5 years following the initial event was 14.7% and 19.0%, respectively. In NAIONy, bilateral involvement occurred in 14 of 37 (37.8%) of the series of Deramo and associates,[35] 17 of 43 (39.5%) of the series of Hayreh and associates,[29] and 70 of 169 (41.4%) of the series of Preechawat and associates.[55] Investigators have postulated that fellow eye involvement rate is higher and that time to fellow eye involvement is shorter in NAIONy than NAIONo.

Our study is the first to compare rate of fellow eye involvement in NAIONy directly to a cohort of patients with NAIONo. Table 3 summarizes the results, with a statistically significant difference in bilaterality rate between groups (46/108 [42.6%] patients with NAIONy, compared to 32/108 [29.6%] patients with NAIONo, chi-square test, P = .047) at a median follow-up for each group of 6 months. Only 3 patients had bilateral involvement at onset, the remainder in both groups having fellow eye involvement during the observation period. Median time between episodes for NAIONy was 12 months (mean 28.9 [range 1-216]) and for NAIONo, 7.5 months (mean 22.8, [range 1-196]); the difference was not significant (P = .16, Wilcoxon rank sum test).

We therefore confirmed a higher bilaterality rate at final follow-up for NAIONy vs NAIONo, and the rate was similar to that of Preechawat and associates (41.4%).[55] While this is substantially higher than published rates for NAIONo, Kaplan-Meier analysis (Figure 10) did not demonstrate a significant difference between curves, although a separation began to develop at 1 year. We believe this is related to two issues:

1. Duration of follow-up was limited for both groups in our study. Median duration was 6 months in each group, with only 42 of 108 (38.8%) of NAIONy and 32 of 108 (29.6%) of NAIONo patients followed past 1 year. Kaplan-Meier analysis past this point was imprecise, and we could not investigate the potential separation of curves further.
2. Even with this limitation, the majority (24/46 [52.2%] NAIONy, 22/32 [68.8%] NAIONo) of cases developing bilaterality did so within the first year. While the NAIONy 12-month Kaplan-Meier estimate of 41% was in keeping with other studies, the 33% estimate for NAIONo was substantially higher than the previous literature 5-year estimates of 14.7% and 19.0%.[46,47] This may represent referral bias of more aggressive disease to our consultative practice. If this bias is present, we underestimated the difference between groups and the increased risk for second eye involvement in NAIONy.

We attempted to identify risk factors that might predispose to fellow eye involvement more frequently in NAIONy than NAIONo. Fellow eye involvement was associated with diabetes but no other vasculopathic risk factors in the IONDT for NAION in patients over age 50.[47] Preechawat and associates[55] found an association with anemia and diabetes in NAIONy. Tables 4 and 5 illustrate that both diabetes and CRF were associated with a higher risk of fellow eye involvement in our study for NAIONy; smoking demonstrated a trend to significance in univariate analysis (Table 4), but this was not confirmed on multivariable analysis (Table 5). CRF was the only significant association in NAIONo. The presence of other risk factors for development of NAION (anemia, crowded discs) was not associated with increased fellow eye involvement. Our study suggests that diabetes is a more important risk factor for fellow eye involvement in NAIONy than in NAIONo.

Patients with CRF composed a substantial proportion (10/108, 9.3%) of our NAIONy cohort. Accelerated vasculopathy is a well-known characteristic in this patient group, and it seemed to manifest in earlier onset (7 patients under 40, one aged 18), more frequent bilaterality (6 patients, 2 with simultaneous onset), and more severe optic neuropathy (2 eyes no light perception, 1 eye light perception only, and 2 eyes finger count only). The bilaterality rate is similar to that seen by Preechawat and associates (75%).[55] While prior reports have suggested that the optic neuropathy in this setting may occur secondary to a toxic effect of the uremia itself, to acute hypertension, or to hypertensive retinopathy with peripapillary edema, our cases all demonstrated features consistent with NAION, including severe optic disc filling delay in all 6 patients in which FA was performed. The decreased prevalence of crowded discs (12/20, 60%) suggests that the severity of the vasculopathy may potentiate ischemic events with less contribution from the structural component seen in most NAION. This is analogous to the situation in arteritic AION (due to giant cell arteritis), in which crowded discs play a much lesser role, presumably also due to more severe vasculopathy. We believe that the combination of early and long-standing hypertension (seen in 6/10 of our patients) with lipohyalinosis of optic nerve vasculature, subsequent chronic hypotension and anemia (seen in all of our cases), and marked fluctuations in fluid dynamics and perfusion pressure related to dialysis predispose to early and severe optic disc ischemia.

A unique feature of our study is the use of early FA filling views of the optic disc to confirm ischemia. Filling delay is a consistent feature in overt NAIONo (75.6%)[20]; segmental early hyperfluorescence is also a common pattern (53.7%).[17] Peripapillary choroidal filling delay is seen in 26.8% in NAIONo, but whereas optic disc filling delay and segmental early hyperfluorescence are not seen in normal controls, this mild choroidal delay is seen in 41.9% of normal controls.[17] In this series of NAIONy, optic disc filling delay was seen in 44 of 54 eyes (81.5%) with NAIONy; early segmental hyperfluorescence was present in 26 of 54 (48.1%), and peripapillary choroidal filling delay in 12 of 54 (22.2%), all paralleling NAIONo. Chronic renal failure patients showed a similar profile (Table 6). Optic disc filling delay and segmental early hyperfluorescence are not features of nonischemic optic disc edema.[20] This is an important factor in confirming that the diagnosis of NAION was accurate in these young patients. However, we presume that ischemia may be present without the overt infarction that occurs in NAION. Hayreh and Zimmerman[70] have proposed this concept in conjunction with reports of optic disc edema without optic nerve dysfunction, which eventually progressed to overt NAION (see above). One of our cases had clear-cut FA features of optic disc ischemia in the face of normal optic nerve function 2 weeks prior to development of a classic NAION syndrome. To our knowledge, optic disc filling delay in this clinical scenario has not previously been documented. We propose that these findings aid in explanation of the diabetic papillopathy syndrome.

DIABETIC PAPILLOPATHY

As noted above, Gordon and associates,[67] Almog and Goldstein,[69] and Hayreh and Zimmerman[70] all reported that some of the cases of optic disc edema in this scenario resolved without the development of overt NAION, leaving either a normal disc or one with slight pallor but no clinically significant optic nerve dysfunction. The implication, based on the patients' vasculopathic risk factors, presence of NAION in fellow eyes, and lack of other cause for optic disc edema, was that it was a manifestation of reversible ischemia. Fluorescein angiography findings in our series support this concept. Seven of 10 (70.0%, comparable to the rate seen in NAION, 75.6%) eyes showed evidence of optic disc filling delay consistent with ischemia, and 4 of 10 (40.0%) demonstrated similar segmental early hyperfluorescence, in the absence of significant optic nerve dysfunction. Only one of these eyes went on to NAION, some 2 years after resolution of optic disc edema. All patients had crowded discs. Ten of 12 manifested diabetic retinopathy. We believe that the diabetic papillopathy syndrome is a manifestation of relatively mild and usually reversible optic disc ischemia.

The prominent optic disc surface vascular dilation and the longer duration of optic disc edema (median, 5 months) remain unexplained. They do not appear to be related solely to young age, as the cohort of NAIONy patients did not demonstrate these features. Retinal venous stasis was not shown on our FA studies. The phenomenon of "luxury perfusion," the result of shunting of blood flow from the ischemic region to a more preserved region of the optic disc, has been proposed as an explanation for the occasional case of prominent vascular dilation in NAION,[24,77] and possibly, by extension, this mechanism could be a contributory factor for this aspect of diabetic papillopathy. Alternatively, the coexistence of diabetic retinopathy in most cases raises the question of associated peripapillary microvasculopathy contributing to increased optic disc surface vasocongestion. Prolonged edema might also be explained by this phenomenon. The lack of overt infarction with subsequent loss of optic disc tissue and reduced compartment syndrome ("auto-decompression") might also explain slower resolution of edema. None of these theories have been tested.

CONCLUSION

This study is the first to compare a cohort of NAIONy patients to a contemporary group with NAIONo. The data confirm these original hypotheses:

1. NAION is not uncommon under age 50.
2. NAIONy has a significantly higher rate of fellow eye involvement than NAION, and the higher rate is associated with diabetes.
3. Fluorescein angiography in NAIONy demonstrates features paralleling NAIONo and consistent with ischemia.
4. The clinical and risk factor profile in NAIONy differs somewhat from NAIONo in that CRF and migraine are more frequent, although many features are similar; the subset of NAIONy with CRF demonstrates more frequently severe and bilateral optic neuropathy.
5. Fluorescein angiography in diabetic papillopathy and in pre-NAION optic disc edema confirms a pattern consistent with ischemia.

6. Optic disc ischemia in patients under 50 years of age encompasses a spectrum ranging from optic disc edema without optic nerve dysfunction to overt infarction (NAION) with permanent visual field loss; the ischemia may be identified in all forms by the characteristic optic disc early filling delay seen on FA.

ACKNOWLEDGMENTS

Funding/Support: Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Financial Disclosures: Dr Arnold has received lecture fees from Pfizer, Inc. Dr Costa and Dr Dumitrasco have no disclosures.

Contributions of Authors: *Design of study* (A.A.); *conduct of study* (A.A., R.C., O.D.); *data collection, management, analysis, and interpretation* (A.A., R.C., O.D.); *preparation of manuscript* (A.A.); *review and approval of manuscript* (A.A., R.C., O.D.)

Other Acknowledgments: Statistical consultation was provided by Fei Yu, PhD, Jules Stein Eye Institute, UCLA Department of Ophthalmology and Department of Biostatistics, UCLA School of Public Health. One case for study was provided by Lynn K. Gordon, MD, PhD, Jules Stein Eye Institute, UCLA Department of Ophthalmology.

REFERENCES

1. Arnold AC. Ischemic optic neuropathy. In: Miller NR, Newman NJ, eds. *Walsh & Hoyt's Clinical Neuro-Ophthalmology*. Vol 1. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:349-384.
2. Spencer WH, Hoyt WF. A fatal case of giant-cell arteritis (temporal or cranial arteritis) with ocular involvement. *Arch Ophthalmol* 1960;64(6):862-867.
3. MacFaul PA. Ciliary artery involvement in giant cell arteritis. *Br J Ophthalmol* 1967;51(8):505-512.
4. Henkind P, Charles NC, Pearson J. Histopathology of ischemic optic neuropathy. *Am J Ophthalmol* 1970;69(1):78-90.
5. Knox DL, Duke JR. Slowly progressive ischemic optic neuropathy. A clinicopathologic case report. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75(5):1065-1068.
6. Lieberman MF, Shahi A, Green WR. Embolic ischemic optic neuropathy. *Am J Ophthalmol* 1978;86(2):206-210.
7. Rootman J, Butler D. Ischaemic optic neuropathy—a combined mechanism. *Br J Ophthalmol* 1980;64(11):826-831.
8. Quigley HA, Miller NR, Green WR. The pattern of optic nerve fiber loss in anterior ischemic optic neuropathy. *Am J Ophthalmol* 1985;100(6):769-776.
9. Levin LA, Louhab A. Apoptosis of retinal ganglion cells in anterior ischemic optic neuropathy. *Arch Ophthalmol* 1996;114(4):488-491.
10. Tesser RA, Niendorf ER, Levin LA**.** The morphology of an infarct in nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2003;110(10):2031-2035.
11. Knox DL, Kerrison JB, Green WR. Histopathologic studies of ischemic optic neuropathy. *Trans Am Ophthalmol Soc* 2000;98:203-222.
12. Flaharty PM, Sergott RC, Lieb W, Bosley TM, Savino PJ. Optic nerve sheath decompression may improve blood flow in anterior ischemic optic neuropathy. *Ophthalmology* 1993;100(3):297-302.
13. Hayreh SS, Beach KW. [Discussion of: Flaharty PM, Sergott RC, Lieb W, Bosley TM, Savino PJ. Optic nerve sheath decompression may improve blood flow in anterior ischemic optic neuropathy]. *Ophthalmology* 1993;100(3):303-305.
14. Arnold AC. Pathogenesis of nonarteritic anterior ischemic optic neuropathy. *J Neuro-Ophthalmol* 2003;23(2):157-163.
15. Eagling EM, Sanders MD, Miller SJH. Ischaemic papillopathy. Clinical and fluorescein angiographic review of forty cases. *Br J Ophthalmol* 1974;58(12):990-1008.
16. Hayreh SS. Anterior ischemic optic neuropathy. II. Fundus on ophthalmoscopy and fluorescein angiography. *Br J Ophthalmol* 1974;58(12):964-980.
17. Arnold AC, Hepler RS. Fluorescein angiography in acute anterior ischemic optic neuropathy. *Am J Ophthalmol* 1994;117(2):222-230.
18. Mack HG, O'Day J, Currie JN. Delayed choroidal perfusion in giant cell arteritis. *J Clin Neuro-Ophthalmol* 1991;11(4):221-227.
19. Siatkowski RM, Gass JDM, Glaser JS, et al. Fluorescein angiography in the diagnosis of giant cell arteritis. *Am J Ophthalmol* 1993;115(1):57-63.
20. Arnold AC, Badr M, Hepler RS. Fluorescein angiography in nonischemic optic disc edema. *Arch Ophthalmol* 1996;114(3):293-298.
21. Feit RH, Tomsak RL, Ellenberger C. Structural factors in the pathogenesis of ischemic optic neuropathy. *Am J Ophthalmol* 1984;98(1):105-108.
22. Beck RW, Savino PJ, Repka MX, Schatz NJ, Sergott RC. Optic disc structure in anterior ischemic optic neuropathy. *Ophthalmology* 1984;91(11):1334-1337.
23. Doro S, Lessell S. Cup-disc ratio and ischemic optic neuropathy. *Arch Ophthalmol* 1985;103(8):1143-1144.
24. Burde RM. Optic disk risk factors for nonarteritic anterior ischemic optic neuropathy**.** *Am J Ophthalmol* 1993;116(6):759-764.
25. Boghen DR, Glaser JS. Ischaemic optic neuropathy. The clinical profile and natural history. *Brain* 1975;98(4):689-708.
26. Repka MX, Savino PJ, Schatz NJ, Sergott RC. Clinical profile and long-term implications of anterior ischemic optic neuropathy. *Am J Ophthalmol* 1983;96(4):478-483.

27. Guyer DR, Miller NR, Auer CL, Fine SL. The risk of cerebrovascular and cardiovascular disease in patients with anterior ischemic optic neuropathy. *Arch Ophthalmol* 1985;103(8):1136-1142.
28. Ischemic Optic Neuropathy Decompression Trial Research Group. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. *Arch Ophthalmol* 1996;114(11):1366-1374.
29. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1994;118(6):766-780.
30. Jacobson DM, Vierkant RA, Belongia EA. Nonarteritic anterior ischemic optic neuropathy. A case-control study of potential risk factors. *Arch Ophthalmol* 1997;115(11):1403-1407.
31. Salomon O, Huna-Baron R, Kurtz S, et al. Analysis of prothrombotic and vascular risk factors in patients with nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 1999;106(4):739-742.
32. Giuffre G. Hematological risk factors for anterior ischemic optic neuropathy. *Neuro-Ophthalmology* 1990;10(4):197-203.
33. Talks SJ, Chong NH, Gibson JM, et al. Fibrinogen, cholesterol, and smoking as risk factors for non-arteritic anterior ischaemic optic neuropathy. *Eye* 1995;9(1):85-88.
34. Chung SM, Gay CA, McCrary JA. Nonarteritic anterior ischemic optic neuropathy. The impact of tobacco use. *Ophthalmology* 1994;101(4):779-782.
35. Deramo VA, Sergott RC, Augsburger JJ, Foroozan R, Savino PJ, Leone A. Ischemic optic neuropathy as the first manifestation of elevated cholesterol levels in young patients. *Ophthalmology* 2003;110(5):1041-1045.
36. Biousse V, Kerrison JB, Newman NJ. Is non-arteritic anterior ischaemic optic neuropathy related to homocysteine? *Br J Ophthalmol* 2000;84(5):554.
37. Pianka P, Almog Y, Man O, et al. Hyperhomocystinemia in patients with nonarteritic anterior ischemic optic neuropathy, central retinal artery occlusion, and central retinal vein occlusion. *Ophthalmology* 2000;107(8):1588-1592.
38. Salomon O, Rosenberg N, Steinberg DM, et al. Nonarteritic anterior ischemic optic neuropathy is associated with a specific platelet polymorphism located on the glycoprotein Ibalpha gene. *Ophthalmology* 2004 Jan;111(1):184-188.
39. Weinstein JM, Feman SS. Ischemic optic neuropathy in migraine. *Arch Ophthalmol* 1982;100(7):1097-1100.
40. Katz B, Bamford CR. Migrainous ischemic optic neuropathy. *Neurology* 1985;35(1):112-114.
41. Hayreh SS, Podhajsky PA, Zimmerman B. Ipsilateral recurrence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 2001;132(5):734-742.
42. Beri M, Klugman MR, Kohler JA, Hayreh SS. Anterior ischemic optic neuropathy. VII. Incidence of bilaterality and various influencing factors. *Ophthalmology* 1987;94(8):1020-1028.
43. Hayreh SS. Anterior ischemic optic neuropathy. Differentiation of arteritic from non-arteritic type and its management. *Eye* 1990;4(1):25-41.
44. Boone MI, Massry GG, Frankel RA, et al. Visual outcome in bilateral nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 1996;103(10):1223-1228.
45. WuDunn D, Zimmerman K, Sadun AA, et al. Comparison of visual function in fellow eyes after bilateral nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 1997;104(1):104-111.
46. Beck RW, Hayreh SS, Podhajsky PA, Tan ES, Moke PS. Aspirin therapy in nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997;123(2):212-217.
47. Newman NJ, Scherer R, Langenberg P, et al. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. *Am J Ophthalmol* 2002;134(3):317-328.
48. Lavin PJM, Ellenberger C. Recurrent ischemic optic neuropathy. *Neuro-Ophthalmology* 1983;3(3):193-198.
49. Beck RW, Savino PJ, Schatz NJ, Smith CH, Sergott RC. Anterior ischaemic optic neuropathy. Recurrent episodes in the same eye. *Br J Ophthalmol* 1983;67(10):705-709.
50. Borchert M, Lessell S. Progressive and recurrent nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1988;106(4):443-449.
51. Dutton JJ, Burde RM. Anterior ischemic optic neuropathy of the young. *J Clin Neuro-Ophthalmol* 1983;3(2):137-146.
52. Hamed LM, Purvin V, Rosenberg M. Recurrent anterior ischemic optic neuropathy in young adults. *J Clin Neuro-Ophthalmol* 1988;8(4):239-246.
53. Josef JM, Burde RM. Ischemic optic neuropathy of the young. *J Clin Neuro-Ophthalmol* 1988;8(4):247-248.
54. Janaky M, Fulop Z, Palffy A, Benedek K, Benedek G. Non-arteritic ischaemic optic neuropathy (NAION) in patients under 50 years of age. *Acta Ophthalmol Scand* 2005;83(4):499-503.
55. Preechawat P, Bruce BB, Newman NJ, Biousse V. Anterior ischemic optic neuropathy in patients younger than 50 years. *Am J Ophthalmol* 2007;144(6):953-960.
56. Servilla KS, Groggel GC. Anterior ischemic optic neuropathy as a complication of hemodialysis. *Am J Kidney Dis* 1986;8(1):61-63.
57. Hamed LM, Winward KE, Glaser JS, et al. Optic neuropathy in uremia. *Am J Ophthalmol* 1989;108(1):30-35.
58. Michaelson C, Behrens M, Odel J. Bilateral anterior ischaemic optic neuropathy associated with optic disc drusen and systemic hypotension. *Br J Ophthalmol* 1989;73(9):762-764.
59. Haider S, Astbury NJ, Hamilton DV. Optic neuropathy in uraemic patients on dialysis. *Eye* 1993;7(1):148-151.
60. Connolly SE, Gordon KB, Horton JC. Salvage of vision after hypotension-induced ischemic optic neuropathy. *Am J Ophthalmol* 1994;117(2):235-242.

61. Knox DL, Hanneken AM, Hollows FC, et al. Uremic optic neuropathy. *Arch Ophthalmol* 1988;106(1):50-54.
62. Saini JS, Jain IS, Dhar S, et al. Uremic optic neuropathy. *J Clin Neuro-Ophthalmol* 1989;9(2):131-133.
63. Taylor D, Ramsay J, Day S, et al. Infarction of the optic nerve head in children with accelerated hypertension. *Br J Ophthalmol* 1981;65(3):153-160.
64. Hayreh SS. Anterior ischemic optic neuropathy. VIII. Clinical features and pathogenesis of post-hemorrhagic amaurosis. *Ophthalmology* 1987;94(11):1488-1502.
65. Johnson MW, Kincaid MC, Trobe JD. Bilateral optic nerve infarctions after blood loss and hypotension. *Ophthalmology* 1987;94(12):1577-1584.
66. Hayreh SS. Anterior ischemic optic neuropathy V. Optic disc edema as an early sign. *Arch Ophthalmol* 1981;99(6):1030-1040.
67. Gordon RN, Burde RM, Slamovits T. Asymptomatic optic disc edema. *J Neuro-Ophthalmol* 1997;17(1):29-32.
68. Prenner JL, Sharma A, Ibarra MS, Maguire AM, Volpe NJ. Prolonged premonitory optic disc signs in anterior ischemic optic neuropathy. *J Neuro-Ophthalmol* 2002;22(2):110-112.
69. Almog Y, Goldstein M. Visual outcome in eyes with asymptomatic optic disc edema. *J Neuro-Ophthalmol* 2003;23(3):204-207.
70. Hayreh SS, Zimmerman MB. Incipient nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2007;114(9):1763-1772.
71. Lubow M, Makley TA. Pseudopapilledema of juvenile diabetes mellitus. *Arch Ophthalmol* 1971;85(4):417-422.
72. Appen RE, Chandra SR, Klein R, Myers FL. Diabetic papillopathy. *Am J Ophthalmol* 1980;90(2):203-209.
73. Barr CC, Glaser JS, Blankenship G. Acute disc swelling in juvenile diabetes. Clinical profile and natural history of 12 cases. *Arch Ophthalmo*l 1980;98(12):2185-2192.
74. Pavan PR, Aiello LM, Wafai MZ, Briones JC, Sebestyen JG, Bradbury MJ. Optic disc edema in juvenile-onset diabetes. *Arch Ophthalmol* 1980;98(12):2193-2195.
75. Hayreh SS, Zahoruk RM. Anterior ischemic optic neuropathy. VI. In juvenile diabetics. *Ophthalmologica* 1981;182(1):13-28.
76. Regillo CD, Brown GC, Savino PJ, et al. Diabetic papillopathy. Patient characteristics and fundus findings. *Arch Ophthalmol* 1995;113(7):889-895.
77. Smith JL. Pseudohemangioma of the optic disc following ischemic optic neuropathy. *J Clin Neuro-Ophthalmol* 1985;5(2):81-89.
78. Hayreh SS, Zimmerman MB. Nonateritic anterior ischemic optic neuropathy: clinical characteristics in diabetic patients versus nondiabetic patients. *Ophthalmology* 2008;115(10):1818-1825.
79. Rizzo JF III, Lessell S. Optic neuritis and ischemic optic neuropathy. Overlapping clinical profiles. *Arch Ophthalmol* 1991;109(9):1668-1672.
80. Rizzo JF III, Andreoli CM, Rabinov JD. Use of magnetic resonance imaging to differentiate optic neuritis and nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002;109(9):1679-1684.
81. Logan JFJ, Chakravarthy U, Hughes AE, Patterson CC, Jackson JA, Rankin SJA. Evidence for association of endothelial nitric oxide synthase gene in subjects with glaucoma and a history of migraine. *Invest Ophthalmol Vis Sci* 2005;46(9):3221-3226.
82. Katz B. Bilateral sequential migrainous ischemic optic neuropathy. *Am J Ophthalmol* 1985;99(4):489.
83. Jonas JB, Gabriele GC, Naumann GOH. Anterior ischemic optic neuropathy: nonarteritic form in small and giant cell arteritis in normal sized optic discs. *Int Ophthalmol* 1988;12(2):119-125.
84. Kline LB. Progression of visual defects in ischemic optic neuropathy. *Am J Ophthalmol* 1988;106(2):199-203.
85. Sergott RC, Cohen MS, Bosley TM, Savino PJ. Optic nerve sheath decompression may improve the progressive form of ischemic optic neuropathy. *Arch Ophthalmol* 1989;107(12):1743-1754.