

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Ocular Thrombosis: A Hypercoagulable Disease

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H&O What conditions comprise ocular thrombosis?

CJG Ocular thrombosis includes central and branch retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), amaurosis fugax (AF), and nonarteritic ischemic optic neuropathy (NAION), all of which are closely related to coagulation abnormalities. In the United States, branch and central retinal vein occlusions are the second most common retinal vascular diseases, after diabetic retinopathy.¹ In the population-based Beaver Dam Eye study of 4,926 subjects, the prevalence of retinal venous occlusive disease was 0.1%.² In the Australian Blue Mountains Eye Study, the prevalence of retinal occlusive disease was 0.7% in persons 49–60 years of age and 4.6% in subjects older than 80 years.³ The incidence of CRAO is approximately .01%, in 60–65 year-old subjects.¹ The incidence of NAION is estimated to be .003% in men at age 50.⁴ In a prospective study in a Danish community of 481,000, the annual incidence of first AF episodes coming to medical attention was .0086% in men and .0062% in women.⁵

H&O What is the etiology of CRAO, AF, and NAION?

CJG In perhaps the majority of cases of a CRAO, a very small piece of atherosclerotic plaque from an ulcerated carotid artery lesion travels to and lodges in the retinal artery. This thrombus causes AF and/or frank CRAO, or, rarely, NAION. There are also, however, a significant number of cases of these three conditions in patients with normal carotid arteries. Our institution has studied at least 40 such patients. These patients have a variety of reasonably common thrombophilias, including G1691A

Factor V Leiden and G 20210A Prothrombin gene mutations, heritable high factor VIII, homocysteine and the methylenetetrahydrofolate reductase (*MTHFR*) C677T and A1298C mutations, and less commonly, the Lupus Anticoagulant-Antiphospholipid antibody syndrome.^{6,7} It is highly important to diagnose CRAO and AF in patients who suffer retinal arterial events without evidence of carotid artery plaque, erosion, or rupture. Patients with AF, and less commonly, CRAO can be administered thromboprophylaxis with low-molecular weight heparin (enoxaparin [Lovenox, Sanofi-Aventis]) or later warfarin (Coumadin, Bristol-Myers Squibb) if necessary. In AF, thromboprophylaxis usually ameliorates the symptoms of transient monocular blindness.⁸ In patients with CRAO and/or AF, there is a very high risk of ischemic stroke if a thrombus travels to the brain instead of a retinal artery. Therefore, it is recommended that patients with CRAO or AF have a carotid and vertebral Doppler sonogram. If this assessment is negative for atherosclerotic plaque, then it is necessary to assess the patient for the major gene thrombophilia-hypofibrinolysis, and to consider anticoagulation.⁸

In CRAO, where there is an atherosclerotic component, clopidogrel bisulfate (Plavix, Sanofi-Aventis/Bristol-Myers Squibb)⁹ or tirofiban (Aggrastat, Merck),¹⁰ which affect platelet aggregation, have utility.

The pathoetiology of CRVO includes many of the same inherited thrombophilias pathoetiological for CRAO, AF, and NAION, such as heritable high factor VIII, the Factor V Leiden mutation, *MTHFR* mutation with high homocysteine, and, more commonly than in CRAO, proteins C and S and antithrombin III mutations.⁷ Additionally, in CRVO, it is fairly common to observe 4G homozygosity of the plasminogen activator inhibitor (*PAI-1*) gene, which is associated with hyperfibrinolysis and a high level of activity of the *PAI-1* gene product, plasminogen activator inhibitor activity (PAI-Fx).⁷

H&O How does exogenous estrogen affect the risk of developing ocular thrombosis?

CJG Very often in cases of CRVO, CRAO, NAION, and AF we see an interaction between the major gene thrombophilias and exogenous estrogens, typically hormone replacement therapy and estrogen-containing oral contraceptives.^{7,10,11} For example, heterozygosity for the Factor V Leiden mutation might put a patient at an 8-fold increased risk of clotting, but hormone replacement therapy with estrogen increases the risk approximately 6-fold, for a combined risk that is approximately 50 times greater than that of the general population. A significant proportion of the patients we have seen in our center with AF, CRAO, CRVO, or NAION have a major gene thrombophilia, with the likelihood of thrombosis exacerbated by exogenous estrogen and occasionally by the physiologic hyperestrogenemia of pregnancy.^{6,7,11}

H&O What evidence exists to support the hypothesis that ocular thrombosis is a hypercoagulable disorder?

CJG The evidence to support the hypothesis that ocular thrombosis can often be attributed to hypercoagulable disorders comes from published data from our laboratory and many others,^{1,6-8, 11-19} which show that the major gene mutations associated with thrombophilias and hypofibrinolysis are strikingly enriched in patients with CRVO, CRAO, AF, and NAION. These ocular thrombotic events that occur are powerfully augmented by a known exogenous stimulus to thrombosis, exogenous estrogen. If an ophthalmologist or primary-care physician sees a patient who has developed CRVO, CRAO, AF, or NAION, particularly a woman receiving exogenous estrogen, the estrogen needs to be stopped immediately, and an investigation must be launched into major gene thrombophilias and hypofibrinolysis as the etiology. Similarly, a patient with CRAO, AF, or NAION who has no evidence of ulcerated plaque on carotid and vertebral Doppler imaging should undergo assessment for these underlying thrombophilias-hypofibrinolyses because one or more is present in almost all such cases.

H&O What evidence exists to contradict this hypothesis?

CJG Rather than contradictory evidence, I would posit that there is some level of opacity in the literature. Most of the literature on CRAO has focused on plaque rupture and cholesterol emboli,²⁰ and not on the equally common coagulation disorders in the absence of plaque rupture

and without cholesterol emboli. Most of the literature on CRAO, AF, and NAION in the absence of carotid plaque strongly agrees with the linkage between these conditions and prothrombotic inherited traits.^{1,13-18,21,22} Regarding CRVO, the pathoetiologic picture is less clear and it requires some qualification. There is a strong difference between CRVO occurring before and after age 55. Before age 55, surely before age 45, the younger the patient, the higher the likelihood that the CRVO is associated with a major gene thrombophilia or hyperfibrinolysis. After age 55, the most likely predictors of this condition are less monolithically thrombotic, and more resemble risk factors for cardiovascular disease: high LDL cholesterol, high triglycerides, low HDL cholesterol, diabetes, and hypertension. The reason for opacity in the literature is that studies have tended to combine age groups or examine risk factors less aggressively in patients over 55 than in patients under 55.

H&O What could occur if ocular thrombosis is left untreated?

CJG In the usual clinical situation for CRVO, CRAO, and NAION, by the time the patient has been examined by the ophthalmologist, the retina and/or ocular nerve has been damaged (often irreversibly). Occlusion in central retinal veins, the central retinal artery, or ciliary artery in NAION leads quickly to a sharp loss of visual acuity. At 3-year follow-up after a CRVO event, 60% of patients with nonischemic CRVO will have visual acuity of 20/125 or less, whereas those with the much more common ischemic CRVO have visual acuity below 20/200, intraretinal hemorrhage, and commonly ocular neovascularization and neovascular glaucoma.¹ In CRVO, the other eye can be affected as much as 7–10% of the time, which can further decrease visual acuity or cause blindness. No consistently effective treatment for CRAO has been reported, and this is particularly marked if symptoms have been present for 24 hours or more.¹ Neovascularization with increased intraocular pressure and hemorrhage is much less common than in CRVO.¹ NAION is characterized primarily by loss of visual acuity, often progressive.²³ In AF without carotid artery plaque ulceration, however, the retinal damage is initially fleeting, and not permanent, and, as we have very recently shown, can be stopped by prompt anticoagulation if thrombophilia-hypofibrinolysis are etiologic.⁸

In AF, CRAO, and NAION, the major problems are loss of vision or visual acuity. However, a second problem in the cohort of patients whose arterial events are unrelated to carotid atherosclerosis is a much higher risk for ischemic thrombosis of the brain, transient ischemic attacks, or ischemic stroke.

H&O At the time a patient presents with symptoms of ocular thrombosis, is it too late to undo its effects?

CJG Historically, by the time a patient presents to the ophthalmologist after the initial sudden loss of vision—it is nearly always sudden—it is too late to reverse the effects. AF attacks are transient and may recur for years without lasting retinal damage. Anticoagulation to resolve underlying thrombophilia-hypofibrinolysis in AF is often successful in preventing monocular transient blindness or progression to frank, persistent, and fixed CRAO.⁸ However, with the majority of ocular thrombotic conditions, when a patient sees a physician, hours, days, or weeks have passed since the initial onset. The thrombus and resulting retinal hypoxia and tissue damage has killed the rods and cones, and the area most severely affected rarely improves. At this point, it is necessary to address the postthrombotic clinical situation.

H&O What further advances in the treatment of ocular thrombosis do you anticipate in the future?

CJG One area of research should be to consider the possibilities of primary or secondary prevention of vascular events in the eye. In patients with unilateral CRVO or unilateral CRAO, AF, or NAION with a documented inherited or acquired thrombophilia or hypofibrinolysis, it is necessary to alert the patient's ophthalmologist or primary-care physician so that a future acute thrombotic event such as ocular thrombosis, transient ischemic attack, or stroke could be rapidly treated with low-molecular weight heparin. Additionally, because the great majority of these disorders are inherited as dominant traits, it is very important after diagnosis to screen all first-degree relatives. Third, it is important to warn all affected women and their first-degree relatives to avoid exogenous estrogen as well as tamoxifen, anastrozole (Arimidex, AstraZeneca), and raloxifene (Evista, Eli Lilly), which will augment a patient's tendency to clot if they have an underlying inherited thrombophilia.²⁴

The presence of multiple thrombophilias-hypofibrinolyses, as in both CRVO and CRAO-AF-NAION^{6-8,16,18,19,25-31} promotes ocular venous and arterial thrombosis,^{17,18} which can lead to acute decompensation of the blood supply to the optic disc.³² In CRVO¹⁸ as well as in CRAO-AF-NAION,⁶ definition of coagulation etiologies is important because, as concluded by Bick and colleagues, "it allows for definition of appropriate acute antithrombotic therapy and subsequent thromboprophylaxis to prevent additional visual loss and also allows identification of those patients with thrombophilias so other thrombotic events can be avoided and appropriate

family members assessed when clinically warranted."¹⁸ The associations of CRVO and CRAO-AF-NAION with thrombophilia has broad clinical implications because these coagulation disorders can cause preventable/reversible deep venous thrombosis and pulmonary emboli,³³ ischemic stroke,³⁴ myocardial infarction,³⁴ osteonecrosis,³⁵ and sporadic and recurrent miscarriage.³⁶

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