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Nonarteritic Anterior Ischemic Optic Neuropathy and Double Thrombophilic Defect: A New Observation

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Key Words

Anterior ischemic optic neuropathy · Thrombophilia · Prothrombin G20210A mutation · Protein S deficiency

Abstract

We report the first case of nonarteritic anterior ischemic neuropathy (NAION) associated with double thrombophilia: protein S deficiency and prothrombin G20210A mutation. A 58-year-old man is presented including the clinical and laboratory findings, cardiovascular profile and thrombophilia screening. The patient presented with 3/10 vision and an inferior altitudinal defect in the right eye. Fundusoscopic examination of the right eye revealed a hyperemic optic disk with blurred superior optic disk border and sectoral nerve fiber layer edema. Complete blood count, erythrocyte sedimentation rate and C-reactive protein were normal, suggesting a NAION. A workup of cardiovascular risk factors revealed hyperlipidemia, arterial hypertension and high-risk asymptomatic coronary artery disease. Due to the family history of deep vein thrombosis in the patient's daughter, a thrombophilia screening was additionally performed. The results revealed a double thrombophilic defect, namely congenital protein S deficiency and heterozygosity for prothrombin G20210A mutation, which were also identified in the patient's daughter. Anticoagulant warfarin therapy was initiated and the patient underwent a triple bypass surgery. At three-month follow-up, the right optic disk edema had resolved, leaving a pale superior optic nerve head. Visual acuity in the right eye had slightly improved to 4/10; however, the dense inferior altitudinal field defect had remained unchanged. The patient is currently treated with warfarin, atorvastatin, irbesartan and metoprolol. This case suggests that the first line of investigation in all patients with NAION involves assessment of cardiovascular risk factors. However, careful history taking will identify NAION patients who are eligible for additional thrombophilia screening: young patients without vasculopathic risk factors, bilateral or

recurrent NAION, idiopathic or recurrent venous thromboembolism (VTE), positive family history of VTE, and VTE in young age or in unusual sites (e.g. cerebral, hepatic, mesenteric, or renal vein).

Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) is a relatively frequent cause of irreversible vision loss in the middle-aged and elderly, with an estimated annual incidence of 2.3 per 100,000 [1]. The risk factors for NAION can be divided into two groups: systemic and ocular. The systemic factors include nocturnal hypotension, sleep apnea syndrome, arterial hypertension, diabetes mellitus, coronary artery disease, arteriosclerosis, hypercholesterolemia and prolonged surgical procedures such as spinal or cardiac bypass surgery [2–4]. A significant association of NAION with a number of ocular and optic nerve head conditions has also been reported. These include small and crowded optic disks, angle closure glaucoma or other causes of markedly raised intraocular pressure, optic disk drusen and cataract extraction [4, 5]. In addition, reports of thrombotic tendencies in some patients with NAION have raised the question of whether there is a causative link between thrombophilia and NAION [2, 6, 7]. Here we present, to the best of our knowledge, the first case of NAION associated with combined protein S deficiency and heterozygosity for prothrombin G20210A mutation.

Case Report

A 58-year-old male patient presented with painless visual loss in his right eye upon awakening in the morning. His best-corrected visual acuity was 3/10 in the right eye and 10/10 in the left eye. A relative afferent pupillary defect was present in the right eye. Funduscopic examination of the right eye revealed a hyperemic optic disk with blurred superior optic disk border, sectoral nerve fiber layer edema, few flame-shaped peripapillary hemorrhages and solitary cotton-wool exudates. Examination of the fellow eye showed a small left optic disk with a cup-disk ratio of 0.2 and slight blurring of the nasal margin, indicating a probable contributory mechanical effect in the pathogenesis of the disease. Visual field testing demonstrated an inferior altitudinal defect in the right eye. Complete blood count, erythrocyte sedimentation rate and C-reactive protein were normal; therefore, the diagnoses of giant cell arteritis or other arteritic optic neuropathies were considered unlikely. The clinical and laboratory findings were compatible with NAION and a complete workup of potential cardiovascular risk factors was ordered. It revealed hyperlipidemia, arterial hypertension and high-risk coronary artery disease. Due to the family history of two episodes of deep vein thrombosis in the patient's daughter (before and during pregnancy), a thrombophilia screening was additionally performed. Laboratory testing included protein C, protein S, antithrombin III, lupus anticoagulant, homocysteine level, anticardiolipin antibodies, activated protein C resistance and prothrombin G20210A mutation. The results revealed a double thrombophilic defect, namely congenital protein S deficiency and heterozygosity for prothrombin G20210A mutation, which were also identified in the patient's daughter. Anticoagulant therapy with warfarin was initiated and the patient also underwent a triple bypass surgery. Follow-up visits were performed at 1 week, 2 weeks and at 1, 3, and 6 months. The patient is still under observation. At three-month follow-up, the right optic disk edema had resolved, leaving a pale superior optic nerve head (atrophy). Visual acuity in the right eye had slightly improved to 4/10; however, the dense inferior altitudinal field defect had remained unchanged. Re-evaluation at six months revealed no significant changes in visual acuity, funduscopic findings and visual field. The patient is currently treated with warfarin (target INR 2.5–3.0), atorvastatin (20 mg/day), irbesartan (150 mg/day) and metoprolol (25 mg twice a day).

Discussion

The contribution of thrombophilic disorders to the pathogenesis of NAION is still under debate. Several observations have suggested that thrombophilic disorders, such as elevated homocysteine, lipoprotein(a) and high frequency of Leiden mutation, may be pathogenetically relevant in the development of NAION by increasing the risk for venous thromboembolism (VTE) [2, 6, 7]. On the other hand, recent studies did not demonstrate an association between NAION and a wide range of thrombophilic risk factors [3]. The principal clinical manifestation of thrombophilia is venous thromboembolism. However, NAION is primarily not a thromboembolic disorder but an arterial ischemic disorder of the optic nerve head [3, 8]. Its pathogenesis has been attributed to optic nerve head hypoperfusion, which is mostly due to nocturnal hypotension [5, 8]. An acute blood flow reduction in the prelaminar portion of the optic disk is generally accepted as the underlying mechanism for the development of NAION [5].

Six-month follow-up of the present patient revealed a slight improvement in visual acuity (from 3/10 to 4/10), which is in consistence with previous reports. In the review by Hayreh and Zimmerman [9] looking at the natural history of visual outcome in NAION, 41% of patients seen within two weeks of symptom onset and with initial visual acuity of 20/70 or worse showed improvement at 6 months. According to the same study, a significant change in visual function after 6 months is unlikely [9]. Therefore, although the patient is still under observation, a further change in his visual acuity or visual field is not expected unless a recurrence of NAION occurs. However, reported episodes of recurrence in the same eye are uncommon and range from 3% to 6.4% [10, 11]. The only significant association for recurrence of NAION was with nocturnal arterial hypotension, while thrombophilia was not associated with recurrence of NAION [3, 10]. Although it is uncommon for NAION to recur in the same eye, it may involve the fellow eye in 14.7% of patients after a median follow-up of 5 years [12]. A history of diabetes has been associated with increased risk of NAION in the fellow eye [13]. In a study by Salomon et al. [3], none of the parameters tested (i.e., gender, age at onset of first NAION, ischemic heart disease, hypercholesterolemia, diabetes, arrhythmia, hypertension, history of stroke, current smoking, crowded disk, and prothrombotic factors) proved to be significant predictors of second eye involvement. According to these findings, the risk of second eye involvement is not increased in the present patient. However, a regular follow-up is suggested, because NAION is a multifactorial disease and other risk factors so far unknown may also play a role.

In conclusion, although we report the first case of NAION associated with a double thrombophilic defect (protein S deficiency and prothrombin G20210A mutation), the inference that NAION was invoked by the thrombophilia is difficult to reconcile with the cardiovascular risk profile and the crowded disks also coexistent in our patient. Hence we suggest that the first line of investigation in all patients with NAION involves assessment of cardiovascular risk factors, in order to detect and treat even life-threatening conditions, such as coronary artery disease, whenever possible. However, it cannot be excluded that thrombogenic tendency may act as a trigger in susceptible individuals [14]. Therefore careful history taking is important, in order to identify NAION patients with thrombophilic defects. Thrombophilia screening is justifiable in

selected NAION cases: young (less than 45 years of age) patients without vasculopathic risk factors, bilateral simultaneous NAION or recurrent NAION in the same eye, idiopathic or recurrent VTE, positive family history of VTE, and VTE in young age or in unusual sites (e.g. cerebral, hepatic, mesenteric, or renal vein) [15, 16].

Disclosure Statement

None of the authors has any conflict of interest with the submission. No financial support was received for this submission.

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