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SHORT REPORT

Anterior ischemic optic neuropathy in a patient with Crohn's disease and aberrant MTHFR and GPIIIa gene variants

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Abstract

Large spectrums of ophthalmic manifestations from the anterior to the posterior segment have been so far reported in patients with inflammatory bowel disease.
Anterior ischemic optic neuropathy is caused by acute ischemic infarction of the optic nerve head and is distinguished in two different types, non-arteritic anterior ischemic optic neuroparhy (NAION) which is the most frequent type and arteritic anterior ischemic optic neuropathy. Non-arteritic anterior ischemic optic neuroparhy may result in severe visual field loss.
We present the case of a 69 year-old man with known history of Crohn's disease that was referred to the Department of Ophthalmology after noticing sudden blurred vision of his left eye. Ophthalmologic examination revealed a corrected visual acuity of 8/10 OS and 10/10 OD. Pupil examination showed a relative afferent pupillary defect of the left pupil and fluoroangiography revealed hyperfluorescence of the left optic disc, indicating edema and NAION attack on his left eye. Genetic analysis showed that the patient was homozygous for MTHFR C677T genetic polymorphism and A1/A2 heterozygous for GPIIIa polymorphism.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic systemic disorder often accompanied by extraintestinal manifestations – almost from all systems – mainly from the skin, joints, liver, vessels and the eyes. The incidence of ophthalmic complications

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varies from 3.5% to 12% according to published literature and they seem to occur more often in Crohn's disease.[1–3] Ophthalmic complications are categorized as primary, secondary and coincidental. Primary are those that are present with activity of the disease and tend to remit with the use of corticosteroids or surgical resection. Secondary are the results of primary complications (e.g cataract due to cortisone use, scleromalacia perforans due to scleritis) and coincidental are frequent complications in the general population that cannot be attributed obligatorily to IBD (e.g conjunctivitis).[4] Eye complications are independent of the extent of bowel involvement and they usually occur in early years of IBD. Rarely, eye manifestations precede the diagnosis of IBD.[5] Their course tends to become parallel with that of the underlying bowel disease.[6] Possible ophthalmic manifestations from the anterior to the posterior segment are concisely the following: eyelid edema, blepharitis, myositis-proptosis, conjuctivitis, episcleritis, scleritis, keratopathy, cataract, iridocyclitis, choroiditis, optic neuritis,[7] ischemic optic neuropathy,[8] insult of retinal vessels, retinal pigment epithelium disturbances, macular edema and hemorrhages and serous retinal detachment.

Anterior ischemic optic neuropathy (AION) is caused by an acute ischemic infarction of the optic nerve head, which is supplied by the short posterior ciliary arteries. There are two different types of AION. Non-arteritic anterior ischemic optic neuroparhy (NAION) which is the most frequent type and arteritic anterior ischemic optic neuropathy (AAION) usually associated with giant cell arteritis.[9]

NAION is the most common acute optic neuropathy in the older population and may result in severe visual acuity or visual field loss. It is characterized by the sudden, usually painless (in 90% of the cases) visual loss, relative afferent pupillary defect and pale optic disc edema. Atrophy of the optic nerve head – generalized or sectorial – supervenes within the next few weeks.[10]

Methylenetetrahydrofolate reductase (MTHFR) catalyzes a critical step in folate metabolism. Polymorphisms, with C677T and A1298C being the most important, result in dysfunction of the enzyme in homozygotes, thus leading to increased homocysteine levels and subsequent atherosclerotic or thromboembolic diseases.[11]

The GPIIIa gene A1/A2 polymorphism of the glycoprotein IIIa on the platelet surface, caused by a T to C nucleotide substitution at position 1565 on chromosome 17q21, results in increased platelet aggregation and increased thrombotic risk.[12]

This is a case report of a 69 year-old man with a known history of Crohn's disease who was referred to the Department of Ophthalmology after noticing sudden blurred vision of his left eye and was subsequently diagnosed with anterior ischemic optic neuropathy.

2. Case report

A 69 year-old man noted painless blurred vision concernig his left eye upon morning awakening and he was referred to our eye clinic. Ophthalmologic examination revealed a corrected visual acuity of 8/10 OS and 10/10 OD. Pupil examination showed a relative afferent pupillary defect of the left pupil. Biomicroscopy of the anterior segment did not show any pathological manifestations. Intraocular pressure was 14 mmHg for both eyes. Dilated fundus examination revealed pale swelling of the left optic disc (Fig. 1) while the vessels, macula and the peripheral retina were normal. Goldmann perimetry showed an inferior visual field loss on the left eye, more prominent temporally. Fluoroangiography revealed hyperfluorescence of the left optic disc, indicating edema.

Patient had a personal history of diabetes, hypertension, hypercholesterolemia, coronary heart disease and Crohn's disease of the terminal ileum. Crohn's disease was diagnosed seven years ago and was on the long-tem quiescent phase with 2 mg/Kg azathioprine maintenance monotherapy. The patient had no history of any abdominal operation or intestinal resection and had no extraintestinal manifestations.

Laboratory tests excluded sarcoidosis and blood dyscrasias. Syphilis screening tests, antinuclear antibodies (ANA), antinuclear cytoplasmic antibodies (ANCA), anti-double stranded DNA antibodies (anti-ds DNA) and anticardiolipin antibody tests were all negative. In addition, routine laboratory tests including hemoglobin, platelet count, and liver function tests were within normal limits, ESR was at 9 mm/h and CRP was negative.

Chest radiography was normal. A magnetic resonance image (MRI) scan of the brain and orbits with gadolinium demonstrated normal optic nerves and no white matter lesions. Ultrasound Doppler of the carotid arteries and neurological examination were also normal. Thrombophilic screening comprising of a wide spectrum of thrombophilic disorders (proteins C, S, antithrombin III, lupus anticoagulant, factors V Leiden and H1299R, II G20210A, MTHFR C677T and A1298C, A1/A2 GPIIIa and I/D ACE) revealed that the patient was homozygous for MTHFR C677T genetic polymorphism and A1/A2 heterozygous for GPIIIa polymorphism. Antithrombin III was 22 mg/dl, protein C 100%, protein S 96%, fibrinogen 220 mg/dl, factor V 90%, prothrombin time was normal at 11 s, folate 7 ng/ml, and vitamin B12 was 486 pg/ml.

The above-mentioned results led us to the conclusion that the patient had experienced NAION attack on his left eye. The patient was subjected to three subtenon injections of beta-methoxazone with a 20-day interval in between.

The visual acuity at the last follow-up evaluation, 1 year after the initial attack, improved to 9/10 for the left eye with ensued optic disc atrophy.

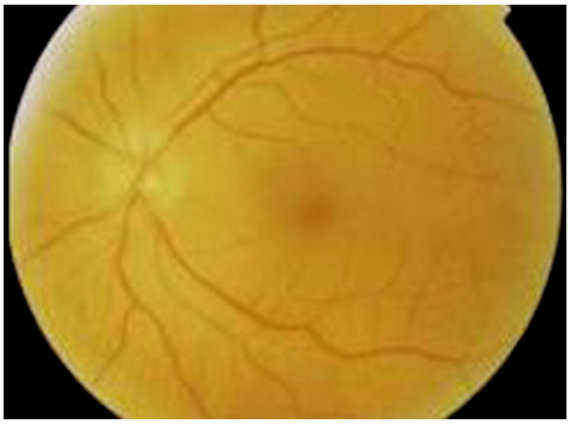

Figure 1 Fundus photography of the patient's left eye, demonstrating optic disc edema.

3. Discussion

NAION is the most common acute optic neuropathy in older age groups with an estimated annual incidence of 2.3 per 100,000.[13] It can affect both eyes in up to 40% of the patients and in most of these cases, second eye involvement occurs within the first year.[14] Recurrent attacks in the same eye, although uncommon, may also occur.[15] The subsequent visual acuity or visual field loss may be devastating and can lead to serious visual impairment. More than half of the patients discover visual loss upon first awakening or when they first use vision critically in the morning.[10]

Differential diagnosis of NAION in general population should include the arteritic form of the disease — mainly associated with giant cell arteritis and other systemic diseases such as polyarteritis nodosa, demyelinating disorders and intracranial and/or intraorbital tumors that may cause optic disc edema.

Arteriosclerosis, hypertension,[16] diabetes mellitus, ischemic heart disease, hypercholesterolemia, "crowded" optic disk,[17] nocturnal hypotension, sleep apnea syndrome,[10,18] erectile dysfunction drugs such as sildenafil,[19] several surgical procedures, for instance liposuction[20] and hemodialysis[21] and thrombophilic disorders have been suggested as risk factors.

The question whether there is an association between NAION and thrombophilic risk factors – inherited or acquired – gives quite controversial results. Salomon et al. did not find any association between NAION and a wide range of thrombophilic risk factors (proteins C, S, AT III, lupus anticoagulant, factors V Leiden, II G20210A and MTHFR C677T). On the other hand, Nagy et al.[9] suggested that hyperfibrinogenemia and factor V Leiden may contribute to the pathogenesis of NAION, while testing for homocysteine and a prothrombin G20210A mutation should be considered in these patients.[13] Beri et al. describe an associated thrombophilic state and non-arteritic anterior ischemic optic neuropathy,[14] and Kuhli-Hattenbach et al.[22] concluded that thrombophilic disorders are associated with the development of NAION in specific subgroups of patients.

A similar ambiguity exists in studies concerning possible association between thrombophilic profile and IBD. Maher et al.[23] found that IBD patients have lower antithrombin III levels than healthy control individuals, while Yilmaz et al.[24] suggest that MTHFR A1298C and ACE I/D polymorphisms may contribute to the pathogenesis of the disease. In addition, the use of salazopyrine may induce folate deficiency and hyperhomocysteinemia.

The genetic screening performed in the patient herein could be of value in terms of therapy as well as of prognosis in Crohn's disease patients. In fact MTHFR genetic polymorphism may influence the outcome of methotrexate therapy by altering the cycle of folic acid donation while GPIIIa polymorphism may be predictive of other possible procoagulant manifestations in other organs. However, data on preventive anticoagulant therapy as a secondary prevention of other possible procoagulant episodes in those patients is still missing.

To our knowledge there is only one previous case report of bilateral ischemic neuropathy of a male patient with Crohn's disease.[25] IBD remains a disease of unknown origin. In Crohn's disease it has been suggested that the multifocal induction of endothelial cell procoagulant activity might be one of the initiating events in the evolution of this condition. Some studies have also suggested that mucosal microvascular changes, including endothelial cell activation and the formation of microthrombi as well as multifocal gastrointestinal infarction are antecedents of epithelial ulceration.[26–28] Although a clear hypothesis of what we think could be the origin is very difficult we could argue that NAION could be another manifestation added in the spectrum of Crohn's disease related procoagulant manifestations in small vessels. This case is favoring a primary NAION–Crohn's disease association and facts supporting this possible scenario are the following: first, Crohn's disease may co-exist with a panel of other autoimmune phenomena or vascular-related diseases. Second in this patient, NAION followed after many years Crohn's disease diagnosis, which is the most frequent prototype in all previously reported Crohn's disease cases with extraintestinal opthalmological manifestations. Third, in a recent study from our center we were able to demonstrate a large spectrum of frequent but also some rare ophthalmological manifestations in IBD patients not previously described in detail.[29] Fourth, there was no probability of drug-induced NAION (i.e salazopyrine) and finally any other known primary cause of NAION was absent in this patient.

Overall, and with logical reservations due to the rarity of the case, we could argue that this patient represents a demonstrable vascular manifestation of this disorder of unknown origin, namely Crohn's disease.

References

1. Sands BE. Crohn's disease. In: Feldman M, Friedman LS, Brant LJ, Sleisenger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disase, pathophysiology diagnosis management. 8th ed. USA: Saunders Elsevier; 2006. p. 2459–90.
2. Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002;**31**:307–27.
3. Stenson WF, Hanauer SB, Cohen RD. Inflammatory bowel disease. In: Yamada T, editor. Textbook of gastroenterology. 5th ed. Hong Kong: Wiley-Blackwell; 2009. p. 1412–3.
4. Knox DL, Schachat AP, Mustonen E. Primary, secondary and coincidential ocular complications of Crohn's disease. *Ophthalmol* 1984;**91**:163–73.
5. Lyon's JL, Rosenbaum JT. Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthropathy. *Arch Ophthalmol* 1997;**115**:61–4.
6. Palli D, Trallori G, Saieva C, Tarantino O, Edili E, D'Albasio G, et al. General and cancer specific mortality of a population based cohort of patients with inflammatory bowel disease. *Gut* 1998;**24**:175.
7. Sedwick LA, Klingele TG, Burde RM, Behrens MM. Optic neuritis in inflammatory bowel disease. *J Clin Neuro-ophthalmol* 1984;**4**: 3–6.
8. Heuer DK, Gager WE, Reeser FH. Ischemic optic neuropathy associated with Crohn's disease. *J Clin Neuro-ophthalmol* 1982;**2**: 175–81.
9. Nagy V, Steiber Z, Takacs L, Vereb G, Berta A, Bereczky Z, et al. Thrombophilic screening for non- arteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:3–8.
10. Mojon DS, Hedges 3rd TR, Ehrenberg B, Karam EZ, Goldblum D, Abou-Chebl A, et al. Association between sleep apnea syndrome and non-arteritic anterior ischemic optic neuropathy. *Arch Ophthalmol* 2002;**120**:601–5.
11. Kluijtmans LA, van den Heuvel LP, Boers GH, Frosst P, Stevens EM, van Oost BA, et al. Molecular genetic analysis in mild

hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. *Am J Hum Genet* 1996;**58**:35–41.
12. Slowik A, Dziedzic T, Turaj W, Pera J, Glodzik-Sobanska L, Szermer P, et al. A2 alelle of GPIIIa gene is a risk factor for stroke caused by large vessel disease in males. *Stroke* 2004;**35**:1589–93.
13. Ischemic Optic Neuropathy Decompression Trial Study Group. Characteristics of patients with non-arteritic anterior ischemic optic neuropathy eligible for the ischemic optic neuropathy decompression trial. *Arch Ophthalmol* 1996;**114**:1366–74.
14. Beri M, Klugman MR, Kohler JA, Hayreh SS. Anterior ischemic optic neuropathy VII: incidence of bilaterality and various influencing factors. *Ophthalmol* 1987;**94**:1020–128.
15. Borchert M, Lessell S. Progressive and recurrent non-arteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1988;**106**: 443–9.
16. Hayreh SS, Joos MK, Podhajsky AP, Long RC. Systemic diseases associated with non-arteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1994;**118**:766–80.
17. Beck WR, Savino JP, Repka XM, Schatz JN, Sergott CR. Optic disk structure in anterior ischemic optic neuropathy. *Ophthalmol* 1984;**91**:1334–7.
18. Behbehani R, Marthews MK, Sergott RC, Savino PJ. Non-arteritic anterior ischemic optic neuropathy in patients with sleep apnea while being treated with continuous positive airway pressure. *Am J Ophthalmol* 2005;**139**:518–21.
19. Lee AG, Newman NJ. Erectile dysfunction drugs and non-arteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 2005;**140**:707–8.
20. Foroozan R, Varon J. Bilateral anterior ischemic optic neuropathy after liposuction. *J Neuro-ophthalmol* 2004;**24**:211–3.
21. Servilla KS, Groggel GC. Anterior ischemic optic neuropathy as a complication of hemodialysis. *Am J Kidney Dis* 1986;**8**:61–3.
22. Kuhli-Hattenbach C, Scharrer I, Luchtenberg M, Hattenbach LO. Selective thrombophilia screening of patients with non-arteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2009;**247**:485–90.
23. Maher MM, Soloma SH. Assesment of thrombophilic abnormalities during the active state of inflammatory bowel disease. *Saudi J Gastroenterol* 2008;**14**:192–7.
24. Yilmaz S, Bayan K, Tüzün Y, Batun S, Altintaş A. A comprehensive analysis of 12 thrombophilic mutations and related parameters in patients with IBD: data from Turkey. *J Thromb Thrombolysis* 2006;**22**:205–12.
25. Heuer DK, Gager WE, Reeser FH. Ischemic optic neuropathy associated with Crohn's disease. *J Clin Neuro ophthalmol* 1982;**2**: 175–81.
26. Wakefield AJ, Sawyerr AM, Dhillon AP, Pittilo RM, Rowles PM, Lewis AA, et al. Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* 1989;**2**:1057–62.
27. Spina L, Saibeni S, Battaglioli T, Peyvandi F, de Franchis R, Vecchi M. Thrombosis in inflammatory bowel diseases: role of inherited thrombophilia. *Am J Gastroenterol* 2005;**100**:2036–41.
28. Magro F, Dinis-Ribeiro M, Araújo FM, Pereira P, Fraga MC, Cunha-Ribeiro LM, et al. High prevalence of combined thrombophilic abnormalities in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2003;**15**:1157–63.
29. Felekis T, Katsanos KH, Kitsanou M, Trakos N, Theopistos V, Christodoulou D, et al. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease; a prospective single center study. *Inflamm Bowel Dis* 2009;**15**: 29–34.