Case report

Secondary hyperhomocysteinemia-related occlusive retinal vasculopathy: A case report

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ABSTRACT

Purpose: To report a case of occlusive retinal vasculopathy, secondary to hyperhomocysteinemia.

Observations: A 43-year-old male was examined at the retina outpatient clinic due to complaints of bilateral decrease in visual acuity. The patient underwent a comprehensive ophthalmological examination, wide-field fundus photographs and fluorescein angiography, as well as spectral domain optical coherence tomography with enhanced-deep imaging. The patient had a significant medical history of chronic kidney disease and progressive bilateral vision loss over the last two years, which worsened in the left eye during the past 3 months. Fundus examination revealed a vitreous hemorrhage in the left eye and bilateral proliferative retinopathy. Blood glucose and systemic blood pressure were unremarkable. Plasma homocysteine was reported at > 500 μmol/L, which is higher than the corrected reference range by age.

Conclusion and Importance: Hyperhomocysteinemia is a rare but well-known disease, capable of accelerating atherosclerotic disease and generating a prothrombotic state that can lead to multiple systemic complications. Despite its low incidence, the disease should be part of the differential diagnosis in patients with bilateral proliferative retinopathy, in the absence of diabetes mellitus and systemic hypertension.

1. Introduction

Hyperhomocysteinemia is a metabolic disease characterized by an inherited defect in the transsulfuration pathway, due to an autosomal recessive mutation of the enzyme cystathionine β-synthase (CBS). This leads to the abnormal accumulation of methionine and its metabolites in the blood and urine. Homocysteine, is a sulfur-containing amino acid; an intermediate product formed during methionine metabolism.\(^1\) It is toxic to the vascular endothelium by inducing endothelial cell loss, increasing platelet adherence, resulting to atherosclerotic lesion formation in the tunica intima of smooth vascular muscles.\(^2,3\)

Skeletal, ocular, neurologic manifestations (intellectual disability), cataract, glaucoma, optic atrophy, ectopia lentis and Marfanoid habitus can be observed at the early stage.\(^7\) Vascular diseases related to thromboembolic and atherosclerotic events, which mainly affect the myocardium, brain, kidneys and pulmonary arteries can also be observed.\(^2\)

Secondary hyperhomocysteinemia is uncommon; however, it can be seen in older patients suffering from diabetes, chronic kidney disease, hypothyroidism, psoriasis, or cancer.\(^5\) Clinical manifestations of secondary hyperhomocysteinemia include vascular disorders like atherosclerosis, thrombosis, ischemic cardiopathy and cerebrovascular accidents (CVA).\(^6\) In the retina, the increased oxidative stress and prothrombotic status induced by the high blood levels of homocysteine,\(^7,8\) tends increase the incidence of venous vascular occlusions\(^1\) and can worsen proliferative retinopathies like diabetic retinopathy\(^5\). In this case report, the authors will describe the clinical manifestations, diagnosis workup and outcome of a 43 years old patient, diagnosed with hyperhomocysteinemia and occlusive vasculopathy, which is not related to diabetic retinopathy.

1.1. Case report

A 43-year-old male patient, was examined at the outpatient clinic, due to complaint of a slowly progressive vision loss in both eyes (OU) for over two years, which became significantly worse during the last

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three months. The loss of vision was associated with the existence of floaters and the patient also complained of a rapid decrease in vision in the left eye (OS). Past medical history included chronic kidney failure due to post-streptococcal glomerulonephritis (treated with peritoneal dialysis and erythropoietin) and well-controlled systemic arterial hypertension (currently treated with beta-blockers and alpha adrenergic-blockers; 115/80 mmHg). The patient was allergic to trimethoprim sulfamethoxazole and denies any relevant surgical and ophthalmologic history. Ophthalmological examination revealed a best corrected visual acuity (BCVA) in the right eye (OD) of 20/200 (1.0 logMAR), and 20/50 (0.4 logMAR) in OS, with a refractive error of myopia and astigmatism.

The superior temporal arterial branch arcade was rounded, with a retinal capillary vessels. The spectral domain optical coherence tomography (SD-OCT) of the macula in OD, showed a posterior vitreous detachment and hyperreflective flecks (sclerosed intraretinal capillary vessels). The superior temporal arterial branch arcade was visible due to the atherosclerotic vascular wall (Fig. 5) in OD. Enhanced depth imaging (EDI) OCT showed the thickening of the optic disk head (Fig. 2).

Fluorescein angiography (FA) showed hyperfluorescence with a leopard spot pattern in the choroid, leakage of the neovascularizations and capillary dropout areas in OU (Figs. 3 and 4). Spectral domain optic coherence tomography (SD-OCT) of the macula in OD, showed a posterior vitreous detachment and hyperreflective flecks (sclerosed intraretinal capillary vessels). The superior temporal arterial branch arcade was visible due to the atherosclerotic vascular wall (Fig. 5) in OD. Enhanced depth imaging (EDI) OCT showed the thickening of the choroidal vessels’ walls and lumen enlargement (Fig. 6).

The patient was initially diagnosed with bilateral proliferative retinopathy secondary to an occlusive retinal vasculopathy. A complete laboratory and hematologic panel was requested to narrow the possible differential diagnoses. The patient underwent a panretinal photocoagulation (PRP) on the same day, which consisted of 1600 burns of moderate intensity, 500-μm size, one-half to one-spot diameter spacing at 0.1-s duration, divided into 2 sessions.

Relevant laboratory analysis showed the following: Complete blood count (CBC): normocytic normochromic anemia. Comprehensive metabolic panel (CMP): elevated blood creatinine levels: 12.9 mg/dL (due to renal damage). Liver function tests: elevated alkaline phosphatase. Albumin and globulin levels were decreased. Lipid panel was unremarkable. Infectious diseases like syphilis (Venereal Disease Research Laboratory (VDRL), fluorescent treponemal antibody absorption (FTA-ABS) and rapid plasma reagin (RPR)) and tuberculosis (purified protein derivative (PPD), erythrocyte sedimentation rate (ESRs)) were ruled out due to negative results. Antinuclear antibodies, rheumatoid factor, anti Smith (anti SM), anti-phospholipid, Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies (C-ANCA), Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA), Complement component 3 (C3) and Complement component 4 (C4), 50% Haemolytic Complement (CH50) Activity of Serum (CH-50%), anti-DNA antibodies, Neutrophil Cytoplasmic Antibodies (P-ANCA), Complement component 3 (C3) and Complement component 4 (C4), 50% Haemolytic Complement (CH50) Activity of Serum (CH-50%), anti-DNA antibodies, anti-RNP, anti-RO and Anti-LA were also negatives. The hematologic panel was negative for Leiden V factor, protein C and S deficiency, and antithrombin III deficiency. A plasma homocysteine determination level, showed an increase of more than 500 μmol/L. Carotid and Orbital Doppler ultrasonography showed a mild stenosis of the carotid and vertebral arteries, with a decrease in the arterial blood flow of the ophthalmic and central retinal arteries. Vitamin B12 and folate oral supplements were introduced at this time.

The final diagnosis was an occlusive retinal vasculopathy secondary to hyperhomocysteinemia. The patient was referred to the cardiology and nephrology department for continued evaluation and treatment. In addition, the patient was seen in the retinal department every three weeks for the first 3 months and once a month thereafter. Repeated FAs were taken in every visit until inactivation of the retinal neovascularization (Fig. 7). During the 12 months follow-up visit, the patient’s BCVA improved to 20/70 in OD (0.5 logMAR) and worsened in OS (20/80, 0.6 logMAR) probably due to cataract evolution. Intraocular pressure was 12 mmHg OU. Slit-lamp examination showed no ruberosis iridis. Fundus examination revealed the absence of retinal neovascularization and NVD in OU (Fig. 8).

2. Discussion

The differential diagnoses of occlusive retinopathies are wide and variable. It requires the exclusion of several diseases like (but not limited to) intermediate uveitis, tuberculosis, immunodeficiency virus retinopathy, Bechet, sarcoidosis, hematologic diseases, systemic lupus erythematosus, Eales disease, among others. An important differential diagnosis to consider in our patient is the existence of advanced hypertensive choriorretinopathy, which could display similar exploratory findings as the ones observed during the
physical examination. Nevertheless, the patient's good control over his blood pressure and adequate medication makes this diagnosis less likely. The authors believe that the existence of atherosclerotic changes in the retina and choroidal vasculature, the occlusive peripheral vasculopathy, RPE atrophy, fibrovascular proliferation, retinal neovascularization, and vitreous hemorrhages are the result of a general prothrombotic state; which was secondary to a homocysteine chorioretinopathy due to systemic hyperhomocysteinemia. Therefore, it is not clear if the metabolic disease was the primary cause of the kidney failure, or if the existence of a previous kidney disease could have worsened the concomitant metabolic disease.

It is not clear to the authors if the chronic kidney disease is related or not to the metabolic diagnosis of hyperhomocysteinemia. Despite the fact that the patient presented a clear history of post-streptococcal glomerulonephritis, it is highly uncommon that patients with hyperhomocysteinemia develop such high levels of blood homocysteine. Therefore, it is not clear if the metabolic disease was the primary cause of the kidney failure, or if the existence of a previous kidney disease could have worsened the concomitant metabolic disease.

Regarding treatment, the patient received a complete treatment of PRP, with laser parameters similar to those used in proliferative diabetic retinopathy (PDR). However, the follow-up and ancillary tests were performed more frequently, in order to ensure complete regression. It is advisable to consider pars plana vitrectomy in similar cases with tractional retinal detachment, or in cases of unsolved or visually debilitating vitreous hemorrhages.

It is important to treat the underlying cause of secondary hyperhomocysteinemia if any exists. Since vitamins B6, B12 and Folate serve as cofactors in the enzymatic pathways for transsulfuration and re-methylation of homocysteine metabolism, the oral supplementation with those nutrients may theoretically improve the homocysteine metabolism, potentially decreasing the incidence of atherosclerotic events and improving arterial endothelial function.

Finally, it is important to always consider the measurement of plasma homocysteine in young patients with clinical evidence of ocular or systemic vascular disease. The targeted lowering of plasma homocysteine could prevent potentially fatal thromboembolic and atherosclerotic events in the future. An in-depth evaluation of secondary causes of hyperhomocysteinemia is always advised in order to improve prognosis.

Fig. 3. A. Fluorescein angiography of the right eye shows hyperfluorescence with a leopard spot pattern in the choroid, leakage of the neovascularization of the optic disk. B. Periphery capillary dropout areas.

Fig. 4. Fluorescein angiography of the left eye shows leakage of the neovascularization of the optic disk and vitreous hemorrhage.

Fig. 5. Spectral domain optic coherence tomography of the right eye shows hyperreflective atherosclerotic vascular wall of the superior temporal arterial branch arcade.
3. Conclusion

The current clinical case suggests that high level of homocysteine in the blood is an independent risk factor for developing occlusive retinal vasculopathy. Hyperhomocysteinemia should be a differential diagnosis when there is a bilateral retinal occlusive vasculopathy with arteriosclerotic changes (similar to advanced hypertensive retinopathies), provided that other uveitic causes had been ruled out according to the patient’s age.

Patient consent

Retrospective clinical case. The patient signed and informed consent form during his admission to the hospital. This report does not contain any personal information that could identify the patient.

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Conflicts of interest

The authors do not have any economic, proprietary or financial interest to disclose in the publication of this paper.

Authorship

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Meeting presentation

This manuscript has never been presented at a meeting or submitted for publication.

Data

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2018.11.005.

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