

Papillophlebitis in a Young Girl Secondary to Homozygous Mutation of MTHFR C677T and A1298C Genotypes

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Central retinal vein occlusion (CRVO) in the young is also known as papillophlebitis and is a rare presentation.¹ Retinal vein occlusion has been known to be associated with many systemic conditions.^{1,2} Association of hyperhomocysteinemia with retinal vein occlusion was reported in the literature.²⁻⁴ There was controversy, however, over whether there was correlation between methylenetetrahydrofolate reductase (MTHFR) gene mutations and hyperhomocysteinemia with the CRVO.⁵⁻⁸ We report a case of young female with unilateral papillophlebitis who was found to have positive homozygous mutations for MTHFR C677T and A1298C genes, which are suggestive of hyperhomocysteinemia.

CASE DESCRIPTION

A 15-year old girl presented with a sudden diminution of vision in the left eye and headache. There was no past history of eye pain, rashes, fever or other systemic illnesses except for secondary amenorrhea of an unknown etiology since 5 months. She was a marathon runner, non-smoker/nonalcoholic. Visual acuity was 20/30 in the right eye (OD) and 20/50 in the left eye (OS). Her intraocular pressure (IOP) was 22 mm Hg OD and 20 mm Hg OS.

Anterior segment examination in both eyes was unremarkable. Fundus examination of the right eye showed normal retinal findings, whereas the left eye demonstrated a hyperemic and mildly edematous optic disc with

diffusely engorged and tortuous retinal veins. There were scattered intraretinal hemorrhages in the macula and in the midperipheral retina. There were faint areas of retinal ischemia and focal whitening in the macula.

Fluorescein angiography (FA) OD revealed no leakage or staining in early or late phases, whereas OS, there was delayed filling of the retinal venous circulation in the early phases and areas of hyperfluorescence and leakage in the late phases. There were no signs of macular edema. Optical coherence tomography (OCT) OS showed a flat foveal region with paramacular retinal thickening (Figure 1A) possibly due to CRVO. She was diagnosed with papillophlebitis (papillitis and nonischemic CRVO) OS. Extensive laboratory workup was ordered to rule out the infectious, inflammatory, thrombophilic and malignant etiologic conditions causing the abnormal eye findings.

By the next day, she noted pain in the left eye with further decrease in the vision from 20/50 to counting fingers (CF) at 3 feet. There was an afferent pupillary defect OS and the fundus examination demonstrated an increase in optic disc edema with progression of intraretinal hemorrhages along the superior and inferior temporal retinal vessels and macular edema. The anterior segment and fundus examination OD was unremarkable at this time. The OCT revealed intraretinal edema and thickening of the macula (Figure 1B). She was treated with intravitreal triamcinolone injection (4 mg/0.5 mL) OS for the advancing macular edema. The complete blood count,

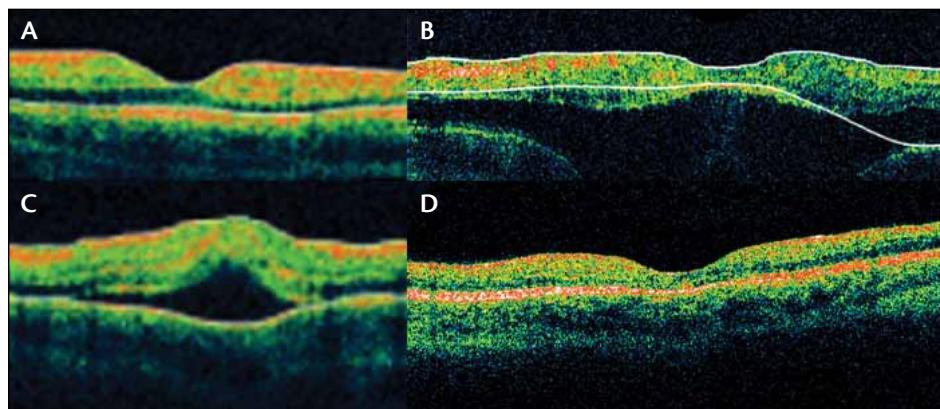


Figure 1. Optical coherence tomography (Stratus OCT) of the left eye showing normal foveal anatomy with mild parafoveal edema at the first visit (A). However, there was macular edema (ME) on second day (B; inverted image). After treatment with the intravitreal triamcinolone, there was marked decrease in macular edema by 1 week (C) followed by the complete resolution of macular edema at 3 months of follow-up (D) (Cirrus OCT).

serum C-reactive protein, angiotensin converting enzyme, lysozyme, estrogen, progesterone, testosterone, follicular stimulating hormone, luteinizing hormone and prolactin levels were normal.

The chest x-ray and magnetic resonance imaging (MRI) of brain and orbits were normal. The antinuclear antibody, and herpes simplex virus antibody titers were negative, and VDRL was nonreactive. The lupus test, PT/PTT, D-dimer, protein C, protein S, and antithrombin III activity, factor V Leiden, prothrombin gene mutation and anticardiolipin antibody (IgM) were negative. DNA mutation analysis of the MTHFR gene revealed positive homozygous C677T mutations and A1298C mutations suggestive of hyperhomocysteinemia. Systemic examination showed mild hypertension and negative workup for deep vein thrombosis and central nervous system vascular thrombosis.

At 1-week follow-up, there was decrease in the eye pain with definite improvement of vision OS from CF to 20/100. On the fundus examination, there was persistent optic disc edema and also CRVO findings OS. The OCT demonstrated minimal intraretinal edema and subfoveal fluid OS (Figure 1C).

At 3-months follow-up, the visual acuity was 20/20 OD and stable at 20/100 OS. Fundus examination OD eye was unremarkable, whereas OS demonstrated no optic disc edema and no clinical macular edema. There were very few residual intraretinal hemorrhages and peripapillary cotton wool spots. The OCT revealed marked decrease of the intraretinal edema with normal foveal region (Figure 1D). The patient was lost to follow-up after moving to another city. We believe that her presumed hyperhomocysteinemia was treated by another physician in that city.

DISCUSSION

Homocysteine is a sulfur amino acid formed from methionine, metabolized to cysteine with help of many vitamins and enzymes, one of which is methylenetetrahydrofolate reductase. Abnormal metabolism of homocysteine leads to its elevated levels in the serum affecting the vascular endothelium, and this leads to hypercoagulable state thereby causing arterial and venous thrombosis.³⁻⁸ There are multiple risk factors

(deficiency of vitamin B12 and folate, chronic renal disease, diabetes mellitus and other proliferative diseases, smoking, drugs [methotrexate, anticonvulsants, metformin, theophylline, omeprazole, and others], and hormones) that increase serum homocysteine levels, of which genotype mutations of MTHFR C677T and A1298C are considered to be important in young people.³⁻⁸ Our patient had no well-known risk factors for the elevation of homocysteine levels, but had positive homozygous mutations of MTHFR C677T and A1298C genes. The papillophlebitis in our patient could be due to the vascular and coagulation system dysfunction secondary to the genotypic mutations in MTHFR C677T and A1298C. In a case-control study in a Chinese population, Gao and associates found a significant association between CRVO and elevated plasma homocysteine levels compared with control patients.⁵ They further found statistically significant correlation between homozygous MTHFR C677T mutations and hyperhomocysteinemia with ischemic CRVO than non-ischemic CRVO patients.⁵ Sottolotta and associates did an investigation on 3114 people to find correlation between homocysteinemia, MTHFR C677T genotype, and CRVO.⁶ They concluded that hyperhomocysteinemia was a possible risk factor for CRVO development, but found no association between CRVO and MTHFR C677T gene mutations.⁶

Prophylactic treatment with anticoagulants was recommended in patients with hyperhomocysteinemia. Our patient was not started initially on anticoagulants due to absence of systemic thromboembolic events, though she had positive mutation of MTHFR genes; however, we felt that after she moved to another city she might be taking the systemic anticoagulants.

Macular edema secondary to CRVO responded to the intravitreal triamcinolone, as reported by Goff and associates, with improvement in vision in 45% of patients at 3 months and in 21% at last follow-up.⁹ However, there was no statistical difference between ischemic and nonischemic CRVO patients at 3 months and at the last follow-up in their 29 patients.⁹ Chang and associates did a retrospective study to investigate the efficacy of intravitreal triamcinolone in 4 patients with papillophlebitis and associated macular edema and found significant improvement in vision in 75% of patients with reduction of central macular thickness from $529 \pm 53 \mu\text{m}$ to $161 \pm 7 \mu\text{m}$ at last follow-up.¹⁰

Mutations in the MTHFR gene are a risk factor for hyperhomocysteinemia in young people, which ultimately leads to hypercoagulable state causing a vascular thromboembolic events including the retinal vessels. Performing extensive laboratory workup is important in such patients to rule out risk factors and etiologic conditions of hyperhomocysteinemia when no other causes have been ruled out. The limitations in our paper include lack of data on serum folate and vitamin B12 levels, no long-term follow-up, and no information on later treatment due to the patient moving to another city. ■

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