

Homocysteine in Retinal Vascular Occlusions

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Abstract: *Elevated plasma homocysteine (hcys) has been associated with a greater risk of heart disease and stroke. A number of studies have suggested that hcys may be a contributing factor to development of various ocular disease. Central retinal vein occlusion (CRVO) is one of the most common vision-threatening retinal vascular diseases, affecting primarily elderly patients. Several studies have demonstrated elevated hcys levels to be a potential risk factor in CRVO, but others failed to find such an association. Also, value of treating an elevated plasma hcys with folic acid for preventing further disease has not been proven. Although secondary prevention of coronary artery disease using this approach has been unsuccessful, trials on primary prevention of stroke and loss of cognitive function with folic acid supplementation appear to be successful. Further trial data are awaited. In this article we will review how systemic and local production of hcys might contribute to the pathogenesis of Retinal Vascular Occlusions.*

Keywords: Homocysteine, Central Retinal Vein Occlusion, Folic acid

1. Introduction

Homocysteine (Hcys) is a sulfur-containing amino acid with a free thiol (sulfhydryl; SH) group, formed from methionine through S-adenosyl methionine in blood.¹ Elevated plasma Hcys has been associated with a greater risk of heart disease² and stroke.³ Ocular complications associated with Hcys include primary open angle glaucoma, diabetic retinopathy, secondary glaucoma, optic atrophy, ARMD, CRVO, Cataract.

Blood levels of hyperhomocysteinemia (HHcy) are age and gender related. Plasma Hcy levels are higher in men than in women⁴ and increase from 10.8 $\mu\text{mol/L}$ at age 40-42 years up to 12.4 $\mu\text{mol/L}$ between 65-67 years.⁵ HHcy is classified as moderate (15-30 $\mu\text{mol/L}$), intermediate (31- 100 $\mu\text{mol/L}$) or severe (>100 $\mu\text{mol/L}$).⁶ HHcy is observed in approximately 5% of the general⁷ population and has been associated with many disorders.⁸

Non-genetic factors for hyperhomocysteinemia include increasing age, various cardiovascular or cerebrovascular diseases, drugs (i.e. anti-epileptics), and lifestyle habits such as nutritional deficits, smoking, high coffee consumption, impaired renal function and poor vitamin B status (particularly folate status but also vitamin B6 and B12 status). In the elderly (age >75 years), hyperhomocysteinemia is generally associated with low folate status or renal impairment.

In this paper, we will explore the various aspects for how Hcys might contribute to the pathogenesis of Retinal Vascular Occlusions.

2. Retinal Vascular Occlusions

Central retinal vein occlusion (CRVO) is one of the most common vision-threatening retinal vascular diseases; it affects primarily elderly patients, resulting in macular edema, vitreous hemorrhage, and neovascular glaucoma. Several studies have demonstrated elevated Hcys levels to be a potential risk factor in CRVO,⁹⁻¹⁶ but others failed to find such an association.¹⁷⁻²³ Thus, the role of Hcys in CRVO remains controversial.

There may be several explanations for these differences. First, age is an important confounding factor; there is evidence showing that Hcys increases with age.²⁴ In studies that demonstrated an association between increased Hcys and CRVO, patients were significantly older than the control subjects.^{9,14,25,26} Second, sex (male or female) is an important confounding factor because Hcys concentrations are greater in males than in females.²⁷ In studies that demonstrated Hcys is an independent risk factor for CRVO, the constituent ratio of male patients was more than that of control subjects.^{11,12,15} Third, patient condition (fasting or non-fasting state) is an important confounding factor because Hcys concentrations are greater in the non-fasting than in the fasting state.²⁴ Two studies that reported an association, non-fasting blood samples were obtained from patients and control subjects in one study, and non-fasting blood samples were obtained from patients and fasting samples from control subjects in another study.^{10,25} Finally, in studies with a retrospective design, patients typically were recruited at variable intervals after onset of CRVO, and the mean time between CRVO occurrence and the determination of Hcys levels ranged from 1 to 69 months, which may have introduced variability in the measured Hcys concentrations..

It now is widely accepted in clinical practice that ischemic CRVO patients and nonischemic CRVO patients exhibit distinct clinical features, complications, courses, and prognoses, and, therefore, should be managed differently. Dong N Wang and B Chu L Xiao L²³ showed that at the finally follow-up examination, three patients with nonischemic CRVO converted to ischemic CRVO. Interestingly, all three patients were defined as hyperhomocysteinemia. This suggests that hyperhomocysteinemia may be a predictor of nonischemic CRVO converted to ischemic CRVO, and of a poor prognosis.

3. Conclusion

The role of Hcys in CRVO is complex. Observational studies have shown that CRVO in general population is associated with raised plasma Hcys concentration. Evidence from controlled trials for any benefit from reduction of Hcys is limited. Further research is required to study whether neuroprotection against elevated Hcys (e.g. memantine) or

lowering of hcys (e.g. fortification) will protect patients from further damage.

There is little data on the use of folic acid in primary prevention of ocular diseases but there is a suggestion from epidemiological studies that a high folate intake and also vitamin B12 supplements may be protective against the development of nuclear cataract.²³ The ongoing Folic Acid and Carotid Intimal Thickness (FACIT) trial has reported significant improvements in cognitive function in subjects aged 50–70 years with baseline elevation of plasma hcys concentrations²⁹ and a useful meta-analysis of eight randomized trials of folic acid supplementation showed reduction in the risk of stroke by 18%.

In the meantime, while the outcomes of further large, randomized trials are awaited, we would recommend measurement of fasting plasma homocysteine in patients with CRVO. The use of folic acid supplementation if hyperhomocystinaemia is identified in these situations is not based on firm evidence but the results from stroke prevention are encouraging.

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