

Asymptomatic Individuals with Vitamin B12 Deficiency Have a Higher Incidence of Homozygosity to MTHFR C677T Mutation and Homocysteinemia

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Background: Although homocysteinemia is associated with a higher risk for cardiovascular disease, treatment of homocysteinemia with folic acid did not result improved outcome. We have shown that homozygotes to MTHFR C677T have higher incidence of B12 deficiency associated with endothelial dysfunction, and could be a better target for clinical trials. The aim of this study was to determine whether subjects with B12 deficiency are more likely to be homozygous for C677T mutation, and whether it is associated with endothelial dysfunction. Methods: We enrolled 100 asymptomatic volunteers with B12 deficiency (<150pM, age 41±12, 48 males). DNA from whole blood was analyzed for MTHFR C677T mutation, and homocysteine measured. Forearm endothelial function using high-resolution ultrasound was performed in 12 homozygotes for C677T before and after treatment with B12 and folic acid, and in 10 non-homozygous controls.

Results: Frequency of homozygosity for the C677T mutation in asymptomatic subjects with B12 deficiency was 28/100 (28%), compared with 47/313 (15%) in a previously published cohort of volunteers with normal B12 levels (p=0.005). Homocysteine level was 21.2±16±M in homozygotes with B12 deficiency compared to 12.3±5.6µM in heterozygotes or subjects without the mutation (p=0.008). After treatment with B12 and folic acid homocysteine decreased to 9.1±2.8µM (p=0.005). Flow mediated dilatation (FMD) of the brachial artery was 5.8±3.1% in homozygotes vs. 5.2±5.7% in non-homozygotes (p=0.8). After treatment with B12 and folic acid, FMD was 6.39±3.5% in homozygotes (p=0.8 vs. baseline).

Conclusions: Asymptomatic subjects with B12 deficiency have a significantly higher incidence of homozygosity to MTHFR C677T mutation and homocysteinemia (28% vs. 15%). In the small group tested, endothelial function of heterozygotes was similar to controls and did not change after treatment. Larger studies are needed to determine whether this group could benefit from treatment with folic acid