Review: MTHFR TT genotype increases risk for coronary heart disease

Klerk M, Verhoef P, Clarke R, et al. **MTHFR 677C →T polymorphism and risk of coronary heart disease: a meta-analysis.** JAMA. 2002;288:2023-31.

QUESTION

Are patients with the methylene tetrahydrofolate reductase (MTHFR) 677C→T genotype at increased risk for coronary heart disease (CHD)?

DATA SOURCES

Studies were identified by searching MEDLINE and Current Contents (to June 2001), reviewing bibliographies of relevant studies and reviews, and consulting with experts in the field.

STUDY SELECTION

Studies were selected if they were case–control studies or nested case–control studies that included data on the MTHFR 677C→T genotype and assessed CHD as an endpoint. Studies were excluded if they had improper case–control design or reported cardiovascular mortality only.

DATA EXTRACTION

Individual patient data were extracted on the MTHFR 677C→T genotype, case–control status, plasma levels of homocysteine and folate, and other cardiovascular risk factors. Data on age, sex, smoking, hypertension, and hypercholesterolemia were extracted where available.

MAIN RESULTS

40 studies (6 unpublished) involving 23 920 patients were included. 22 studies were from Europe (2 prospective), 10 from North America (3 prospective), and 8 from other continents (0 prospective). Patients with the TT genotype had a greater risk for CHD than did patients with the CC genotype (odds ratio [OR] 1.16, 95% CI 1.05 to 1.28). The increased risk for CHD in patients with the CT genotype did not reach statistical significance (OR 1.04, CI 0.98 to 1.10). Significant heterogeneity existed among the studies, primarily accounted for by the continent of origin. There was an increased risk for CHD among patients with the TT compared with the CC genotype in European studies (OR 1.14, CI 1.01 to 1.28) but not North American studies (OR 0.87, CI 0.73 to 1.05). An interaction was seen between MTHFR 677C→T polymorphism and folate status, showing an increased risk for CHD with low folate levels (OR for TT genotype 1.44, CI 1.12 to 1.83) and no increased risk with high folate levels (OR for TT genotype 0.99, CI 0.77 to 1.29). The OR of CHD for the TT genotype was 0.86 (CI 0.67 to 1.10) for prospective studies and 1.21 (CI 1.10 to 1.33) for retrospective studies.

CONCLUSION

Patients with the methylene tetrahydrofolate reductase 677 TT genotype have greater risk for CHD than patients with the CC genotype.

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COMMENTARY

Epidemiologic studies indicate that moderately elevated blood levels of homocysteine are independently predictive of the risk for CHD, both in apparently healthy persons and patients with established atherothrombosis (1). The common 677C→T polymorphism for the gene that encodes the MTHFR enzyme (a key determinant of blood homocysteine levels) is associated with reduced enzyme activity and increased homocysteine levels. Therefore, if moderately elevated homocysteine levels are truly a causal risk factor for atherothrombosis one would expect the TT genotype to be overrepresented in patients with CHD. However, an independent association between the MTHFR TT genotype and CHD risk has not been shown to date, and this has led some investigators to question the validity of the "homocysteine hypothesis" of atherothrombosis (2).

The meta-analysis by Klerk and colleagues is important because it provides, for the first time, convincing evidence of a relation between the MTHFR TT genotype and CHD risk. Furthermore, the association was independent of "conventional" vascular risk factors, although it was strongly modified by folate status; the TT genotype had no adverse effect on cardiovascular risk in patients with normal folate status. Differences in folate status between continents may also explain why a relation between TT genotype and CHD risk was not evident in North American or in prospective studies (most of which were done in North America). Vitamin supplements and folate fortification of food are more widely used in North America than in Europe, as reflected by lower mean homocysteine levels in North American than in European studies and may have masked any association between the TT genotype and CHD risk in the North American studies.

An independent association between the MTHFR TT genotype and CHD was recently confirmed by another meta-analysis (3) and further strengthens the evidence that elevated homocysteine is a cause of cardiovascular disease. However, there is still no role for routine screening for elevated homocysteine or the MTHFR TT genotype. Even if causality of association were proven, screening should only be considered if the results enhance patient care or reduce the burden of cardiovascular disease in a cost-efficient manner (4). In the case of elevated homocysteine or the MTHFR TT genotype, this has not yet been shown.

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