BRIEF COMMUNICATION

Gene–gene interaction between fetal MTHFR 677C>T and transcobalamin 776C>G polymorphisms in human spontaneous abortion

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BACKGROUND: Genetic polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) and transcobalamin (TC) genes influence homocysteine metabolism which in turn may influence the risk of spontaneous abortion. It was hypothesized that there may be a significant interaction between MTHFR and TC genotypes which affects the pathogenesis of spontaneous abortion.

METHODS AND RESULTS: A total of 76 fetal tissue samples from spontaneous abortions between weeks 6 and 20 of pregnancy, and 114 control samples from healthy blood donors were genotyped for the MTHFR 677C>T and 776C>G polymorphisms. Subjects with combined MTHFR 677TT/TC 776GG and combined MTHFR 677TT/TC 776CG genotypes gave an odds ratio for spontaneous abortion of 3.8 (95% confidence interval 1.4–9.9, \( p = 0.005 \)).

CONCLUSIONS: Embryos that have combined MTHFR 677TT and TC 776CG or 776GG genotypes; genotypes that individually are associated with impaired homocysteine metabolism in adults, are at increased risk for spontaneous abortion compared with embryos that have only one of these genotypes.

Key words: folate supplementation/gene linkage/gene polymorphism/homocysteine/spontaneous abortion

Introduction

Gene–gene and gene–environment interactions are supposed to play a crucial role in phenotypic expression of moderate hyperhomocysteinaemia (HHcy), which is a risk factor for neural tube defects (Steegers-Theunissen et al., 1991; Mills et al., 1995) and recurrent embryo loss (Steegers-Theunissen et al., 1992; Wouters et al., 1993; Nelen et al., 2000). The best characterized genetic polymorphism that influences homocysteine metabolism is the methylenetetrahydrofolate reductase (MTHFR) polymorphism at nucleotide position 677 consisting of a C\( \rightarrow \)T transition (677C>T) that results in an alanine to valine substitution in the predicted catalytic domain of MTHFR (Frost et al., 1995). The homozygous 677TT genotype is associated with elevated homocysteine levels, predominantly in individuals with low plasma folate levels (Jacques et al., 1996). Another common genetic polymorphism that influences homocysteine metabolism is a C\( \rightarrow \)G transition at position 776 (776C>G) in the transcobalamin (TC) gene (Zetterberg et al., 2003). The transition results in a substitution of arginine for proline at codon 259 and is the major determinant of the TC phenotypic variability (McCaddon et al., 2001; Namour et al., 2001). TC is the critical transporter that delivers vitamin B\( _{12} \) to the tissues and 776CG and 776GG genotypes are associated with lower TC concentration in plasma (Afman et al., 2001; Namour et al., 2001) and a tendency towards increased homocysteine levels (Namour et al., 2001). We have previously shown, in two separate studies, that fetal MTHFR 677C>T and TC 776C>G polymorphisms influence the risk of spontaneous abortion (Zetterberg et al., 2002a;b). Here, we hypothesized that there may be a significant interaction between the HHCy-associated MTHFR 677TT genotype and the TC 776CG or 776GG genotypes in the pathogenesis of spontaneous abortion.

The study and control groups have been extensively described previously (Zetterberg et al., 2002b).

Materials and methods

The final study group consisted of 76 fetal tissue samples from spontaneous abortions between weeks 6 and 20 of pregnancy (10.4 ±
2.9) with the majority (87%) occurring earlier than week 12. The control group consisted of 114 DNA samples from randomly-chosen healthy blood donors from Crete.

The study was approved by the Ethics Committee at the University Hospital of Heraklion and written informed consent was obtained from the relatives of all participants.

Results

Genotypes for both polymorphisms were available for 76 spontaneously aborted embryos (fetal death between weeks 6 and 20 after conception) and 114 adult controls from the same geographical area (Table I). Three spontaneously aborted embryos had combined homozygous MTHFR 677TT and TC 776GG genotypes while no such subjects were detected among the adult controls ($P = 0.062$, not significant). Twelve spontaneously-aborted embryos had combined MTHFR 677TT and TC 776CG genotypes compared with only seven among the adult controls ($P = 0.046$), resulting in an odds ratio for spontaneous abortion of 2.9 [95% confidence interval (CI) 1.1–7.8] when using remaining genotypes as the comparative group. When grouping subjects with combined MTHFR 677TT and TC 776GG and combined MTHFR 677TT and TC 776CG genotypes, the odds ratio for spontaneous abortion was 3.8 (95% CI 1.4–9.9, $P = 0.005$). No significant differences between aborted embryos and controls were detected for the homozygous 677TT genotype in combination with the wild-type TC genotype (776CC) or the heterozygous TC 776CG and the homozygous TC 776GG genotypes in combination with the wild-type MTHFR genotype (677CC).

Conclusions

In conclusion, embryos that have combined MTHFR 677TT and TC 776CG or 776GG genotypes; genotypes that individually are associated with impaired homocysteine metabolism in adults, are at increased risk for spontaneous abortion compared with embryos that have only one of these genotypes. This indicates a detrimental interaction between the MTHFR 677TT and TC 776CG or 776GG genotypes during embryogenesis and further underscores the linkage between decreased fetal viability and elevated homocysteine concentration that may induce DNA damage, oxidative stress and apoptosis and/or reflect insufficient methylation of crucial metabolites in the developing embryo (Mattson and Shea, 2003). Since the negative effects of these genotypes on homocysteine metabolism can be modified by supplementation with folate and vitamin B$_{12}$, our data support the hypothesis that periconceptual supplementation with B-vitamins may reduce the risk of spontaneous abortion.

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References


