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Methylenetetrahydrofolate Reductase Polymorphisms Are Related to Male Infertility in Brazilian Men

Marcello Machado Gava,[1,2] Elisangela de Oliveira Chagas,[1] Bianca Bianco,[1] Denise Maria Christofolini,[1] Antonio Carlos Lima Pompeo,[2] Sidney Glina,[2] and Caio Parente Barbosa[1]

Objective: The objective of this study was to analyze the distribution of the methylenetetrahydrofolate reductase (*MTHFR*) C677T and A1298C polymorphisms in idiopathic infertile Brazilian patients with nonobstructive azoospermia (NOA) or severe oligozoospermia and fertile Brazilian men as controls to explore the possible association of these polymorphisms and male infertility. *Methods:* A case–control study was carried out, including 156 idiopathic infertile Brazilian patients with NOA ($n = 49$) or severe oligozoospermia ($n = 107$) and 233 fertile men as controls. Polymorphisms C677T and A1298C were studied by quantitative polymerase chain reaction and the results were statistically analyzed. *Results:* The frequency of genotypes *MTHFR* 677CC, 677CT, and 677TT in idiopathic infertile men with NOA were 55.1%, 30.6%, and 14.3% ($p = 0.0305$); 50.6%, 42.0%, and 7.5% ($p = 0.0006$) regarding the severe oligozoospermic men; and 71.7%, 53.0%, and 5.6% in the control group. As for polymorphism A1298C, regarding the NOA group, the frequencies of the 1298AA, 1298AC, and 1298CC genotypes were 53.0%, 28.6%, and 18.4% ($p = 0.0132$); 42.0%, 44.9%, and 13.1% ($p = 0.0188$) among the severe oligozoospermic group; and 55.8%, 38.2%, and 6.0% (14/233) in the control group. *Conclusion:* The data suggest that *MTHFR* C677T and A1298C could be important genetic factors predisposing to infertility in Brazilian infertile men.

Introduction

Infertility is a very common health problem that affects ~15%–20% of couples who attempt pregnancy (Oliva *et al.*, 2001). In almost 50% of infertile couples, the problem is related to the male, and in about 15% of male infertile subjects, genetic abnormalities could be present, including chromosomal aberrations and single gene mutations (Ferlin *et al.*, 2006; Pieri *et al.*, 2002).

Folate is essential for DNA synthesis and methylation reactions and for protein synthesis (Fang and Xiao, 2003). Methylenetetrahydrofolate reductase (*MTHFR*) is a key regulatory enzyme involved in folate metabolism, DNA synthesis, and remethylation reactions. The metabolic pathways of folate can be modified by polymorphisms in relevant genes such as *MTHFR* or by the action of carcinogenic elements, for example, alcohol or tobacco (Lee *et al.*, 2006).

The *MTHFR* gene, located on the short arm of chromosome 1 (1p36.3), presents two common polymorphisms involving nucleotides C677T and A1298C. The change of C for T at position 677 causes the substitution of alanine for valine in the MTHFR protein and a consequent reduction in enzyme activity. The specific activity of the MTHFR enzyme is reduced by 35% in the presence of heterozygosis, genotype C/T, compared with the normal genotype C/C, and by 70% in homozygosis, genotype T/T. Polymorphism A1298C brings about the substitution of a glutamate for a valine, causing a reduction in the enzyme activity that is more effective when in homozygosis (Fross *et al.*, 1995; van der Put *et al.*, 1998).

Low folate coupled with *MTHF*R polymorphisms can alter RNA/DNA synthesis and has the potential to be linked with infertility (Stern *et al.*, 2000). Animal model studies suggest that *MTHFR* plays a critical role in spermatogenesis because of exceptionally higher activity in adult testis than other organs (Chen *et al.*, 2001).

Thus, the objective of the present study was to determine the distribution of the *MTHFR* C677T and A1298C polymorphisms in idiopathic infertile Brazilian patients and controls to explore the possible association of these polymorphisms to male infertility.

Material and Methods

Patients

Among the patients of the Andrology Outpatient Clinic of the Division of Pathological Gynecology and Human

[1]Division of Pathological Gynecology and Human Reproduction, Department of Gynecology and Obstetrics, ABC School of Medicine, Santo André, São Paulo, Brazil.
[2]Division of Urology, Department of Surgery, ABC School of Medicine, Santo André, São Paulo, Brazil.