

Case Report

Case Report: Homozygous C677T MTHFR Gene Mutation in Male with Hypogonadism

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We report a 44-year-old male, who was diagnosed with hypogonadotropic hypogonadism after complaining of erectile dysfunction, depression, and fatigue. He was started on testosterone replacement therapy. He persistently complained of fatigue despite increasing the dose of testosterone over two years and having therapeutic testosterone levels. He was found to have homozygous C677T methylenetetrahydrofolate reductase (MTHFR) gene mutation. After treatment with folate and B12, his symptoms resolve completely. MTHFR is a key enzyme in the folate pathway, and it plays an essential role in homocysteine metabolism. Homozygous C677T individuals have decreased activity of MTHFR enzyme with increased homocysteine levels, which is associated with increased risk of thrombosis. An association has been reported between C677T variant and male infertility. Patients identified to have hyperhomocysteinemia should be treated with B-complex vitamin supplements. Our case emphasizes other possible etiologies for fatigue and erectile dysfunction in a male with hypogonadism on testosterone therapy. Also, it shows possible association between MTHFR gene mutation and male hypogonadism.

1. Introduction

MTHFR is a key enzyme in the folate pathway, and it plays an essential role in homocysteine metabolism. Homozygous C677T individuals have decreased activity of MTHFR enzyme with potentially increased homocysteine levels that are associated with increased risk of venous thrombosis, stroke, coronary artery disease, and recurrent pregnancy loss in females. There have also been reports of association between C677T variant and male infertility.

2. Case Report

We report a case of a 44-year-old male, who was a semi-professional football player in late teenage years, with a history of multiple head concussion between age 15 and 25.

He was diagnosed with hypogonadotropic hypogonadism in 2013, when he complained of erectile dysfunction, depression, generalized fatigue. He was started on testosterone replacement therapy. He persistently complained of fatigue despite increasing the dose of testosterone over two

years and having therapeutic testosterone levels on labs while on therapy.

At that point, he underwent genetic testing, as per patient personal request, which showed homozygous C677T MTHFR gene mutation.

Other relevant labs included folate: 3.1 ng/mL (normal range: 4.2–19.9) and B12: 333 pg/mL (normal range: 210–934).

His hemoglobin was at normal levels, but interestingly, it did not increase as expected with the use of testosterone.

The patient was treated with folate and B12 supplements, which made his symptoms resolve completely (Table 1).

3. Discussion

MTHFR is a key enzyme in the folate pathway, and it plays an essential role in homocysteine metabolism, as shown in Figure 1.

Homozygous C677T individuals have decreased activity of MTHFR enzyme, thus having an increased risk for hyperhomocysteinemia when deficient in folate, vitamin

TABLE 1: Social history.

Smoking	Current smoker, 10 pack-year
Alcohol use	Occasional; a glass of beer or wine on occasions
Recreational drug use	None/never
Physical activity	Exercises for 1 hour 3 days a week; walking or weightlifting
BMI	28

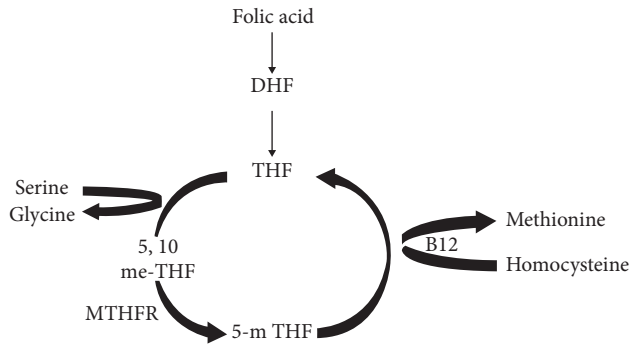


FIGURE 1: Folic acid is reduced to dihydrofolate (DHF) then to tetrahydrofolate (THF). THF is converted to 5,10-methylenetetrahydrofolate (5, 10-me-THF), which is then reduced to 5-methyltetrahydrofolate (5-m-THF) by MTHFR. 5-m-THF is demethylated to complete the folate cycle by donating a carbon into the methionine cycle through the methylation of homocysteine to methionine by methionine synthase and its cofactor vitamin B12.

B12, or pyridoxine [1]. Elevated homocysteine levels are associated with increased risk of venous thromboembolism, strokes, coronary artery disease, and recurrent pregnancy loss [2]. The exact cause of accelerated vascular disease is unclear, but several mechanisms have been suggested, including endothelial cell damage, lipid peroxidation, smooth muscle cell proliferation, downregulation of antithrombotic factors, and upregulation of prothrombotic factors.

Male hypogonadism, defined as decreased testosterone production and/or impaired ability to produce functional sperms, overlaps with male infertility. The association between C677T variant and male infertility has been reported in the literature.

While some studies did not find an association between C677T polymorphism and male infertility [3, 4], Bezold et al. [5] reported that the prevalence of the homozygous C677T mutation was 18.8% in infertile males as compared with 9.5% in normal fertile males. Thus, it was concluded that MTHFR products may play a role in the pathogenesis of male infertility.

Mfady et al. [6] showed that in Jordanians, *MTHFR* C677T polymorphism was associated with male infertility, while *MTHFR* A1298C was not. Similar results were reported by Park et al. [7] in the South Korean population.

Gong et al. [8] conducted a meta-analysis on 26 studies involving 5,575 cases and 5,447 controls. *MTHFR* C677T polymorphism was significantly associated with male infertility in Asians as well as in Caucasians.

Other studies, on the other hand, concluded that there is an association between C677T variant and male infertility in Indian, African, and Southeast Asian populations. Data from

Europe regarding this association are conflicting. The lack of similar association in Western populations could be due to the overall dietary enrichment with folates [9].

Lombardo et al. [10] studied the role of C677T *MTHFR* mutation with subsequent hyperhomocysteinemia in erectile dysfunction. He concluded that hyperhomocysteinemia in homozygous C677T patients may interfere with erection mechanisms and thus cause erectile dysfunction.

Patients identified to have hyperhomocysteinemia should be treated with B-complex vitamin supplements. Initiation of therapy with folic acid, B12, and B6 vitamins tends to normalize homocysteine in 1-2 months. It is unclear whether normalization of homocysteine would improve male infertility or not.

4. Conclusion

Our case emphasizes other important etiologies for fatigue and erectile dysfunction in a male with hypogonadism on testosterone therapy as well as shows the possible association between *MTHFR* gene mutation and male hypogonadism.

Disclosure

This abstract was presented as a poster in AACE 2019 Meeting in Los Angeles.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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