CASE REPORT

Variants of DHFR, MTHFD1, and MTHFR Genes: Relation to CNS Malformations

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Introduction

Congenital central nervous system (CNS) anomalies are a group of heterogeneous diseases affecting approximately 2–3 % of all live births of which neural tube defects (NTDs) are the most frequent.

Case Report

A non-consanguineous couple with CNS anomalies in both the pregnancies was referred for genetic counseling. During her first pregnancy, mild degree hydrocephalous, dilation of the 3rd ventricle, no prominent 4th ventricle, and agenesis of corpus callosum were observed at the 36–37-week ultrasound scan (Fig. 1). She delivered a full-term male baby at 36 and a half weeks and the external appearance revealed occipital encephalocele. A computed tomography (CT) scan image of the brain showed agenesis of corpus callosum and mild to moderate dilation of the supratentorial ventricular system. The baby expired at 2 years of age. The child and the couple had a normal karyotype.

During her second pregnancy, an ultrasound scan at 19–20 weeks revealed occipital encephalocele and hydrocephaly, so the couple opted for termination (Fig. 1). After the postmortem, the external appearance of the head revealed occipital encephalocele and internal appearance revealed inter-parietal meningocele, occipital meningocele, agenesis of corpus callosum, and bilateral ventriculomegaly. The mother was on folic acid supplementation during both pregnancies.

The common genetic variants reported to be responsible for CNS malformations were evaluated. These included 19 bp deletion, G1958A and C677T polymorphisms of dihydrofolate reductase (DHFR), methylene tetrahydrofolate dehydrogenase 1 (MTHFD1), and methylene tetrahydrofolate reductase (MTHFR) genes. Genetic workup of the couple and the fetuses revealed normal genotype for 19 bp deletion of DHFR gene and homozygous AA genotype for the variant allele of MTHFD1 gene. In the case of MTHFR gene, we found heterozygous CT genotype in the husband and the first fetus. However, the wife and the second fetus had a normal CC genotype.

Discussion

DHFR is considered as a potential candidate gene for NTDs [1]. However, in an Irish population, this deletion has been reported to decrease the risk for spina bifida. In the present case, both the parents and fetuses were found to be normal for the 19 bp deletion allele of DHFR gene.

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Fig. 1 Antenatal scans showing different CNS anomalies

MTHFD1 G1958A has been recognized as a maternal risk factor for NTD in various populations [2]. This association was not found in Dutch and British populations. In the present case, both the parents and their fetuses were found to be homozygous (AA) for the variant allele. This is the first report from India finding an association between MTHFD1 G1958A polymorphism and NTD and other associated CNS anomalies. We have screened around 30 couples, with a history of producing children with NTDs, for MTHFD1 polymorphism. Around 50 % mothers and 40 % fathers were found to be homozygous for the variant allele (unpublished data). These findings suggest that this gene variant might be a risk factor for NTDs and other associated CNS anomalies in the Indian population.

Numerous investigations have yielded C677T polymorphism in MTHFR gene to be associated with approximately doubling the risk for NTDs. In the Indian population, most of the reports could not establish this association [3]. In the present case also, the mother and their second fetus were found to carry the normal allele (CC), while father was heterozygous (CT) for this polymorphism.

In conclusion, G1958A polymorphism of MTHFD1 is a risk factor for NTDs and other associated CNS anomalies.

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Conflict of interest The authors declare that there is no conflict of interest.

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