The prevalence of homozygous MTHFR polymorphism(s) in a Turkish university hospital population that necessitated MTHFR polymorphism investigation

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ABSTRACT

Background: Methylenetetrahydrofolate reductase (MTHFR) polymorphisms may cause various medical disorders through different mechanisms. We aimed to determine the allelic frequency and the prevalence of homozygous MTHFR polymorphisms in a tertiary university hospital population that necessitated MTHFR polymorphism investigation owing to various reasons.

Methods: Our study consisted of 10449 patients who necessitated MTHFR polymorphism investigation owing to various reasons (coronary artery diseases, thrombotic events, epilepsy, migraine, repeated miscarriages, various obstetric complications) during 2008-2017.

Results: The allelic frequency of MTHFR C677T and MTHFR A1298C mutations were 0.296 and 0.283 respectively. The prevalence of homozygous MTHFR C677T and MTHFR A1298C polymorphisms were 10.2 % and 11.1 %, respectively.

Conclusion: MTHFR polymorphisms are more frequent than was expected and one should be cautious when drawing disorder specific conclusions.

Keywords: demographic analysis, gene frequency, genetic polymorphism, methylenetetrahydrofolate reductase, Turkey

INTRODUCTION

Methylenetetrahydrofolate reductase (MTHFR) polymorphisms are reportedly to be associated with coronary artery diseases (CAD), thrombotic events, epilepsy, migraine, repeated miscarriages, and various obstetric complications (1-7).

MTHFR is a critical enzyme which plays a role in folate metabolism and participates in the enzyme pathways associated with DNA methylation (8-10). It converts dietary folate (methylenetetrahydrofolate) to active folate, which is the coenzyme that is required by methionine synthase, together with vitamin B12 (8, 10). This pathway is also critical in the methylation of nucleotide/DNA which is important in regular DNA synthesis (11, 12).

MTHFR polymorphisms may cause various medical disorders through different mechanisms. One of the mechanisms is hyperhomocysteinemia, which accompanies endothelial injury of vascular structures of different organs (11, 13). Homocysteine is an endothelial-toxic amino acid which is metabolized through methylation and trans-sulphuration processes. MTHFR polymorphisms also affect DNA synthesis by various routes, one being impaired DNA methylation and another being the accumulation of dietary folate, which is also a toxic material causing endothelial injury. Methylenetetrahydrofolate is converted to dihydrofolate, which in turn is converted to monohydrofolate. This is subsequently reconverted to methylenetetrahydrofolate for the clearance of MTHFR. During this process, translational autoregulation of thymidylate synthase and dihydrofolate reductase, and uridine monophosphate conversion to thymidine monophosphate is impaired, resulting in the formation of tetrameric DNA and related complications (10, 11).

MTHFR polymorphism related pathological conditions necessitate MTHFR polymorphism prevalence studies. However, one must consider the chaotic structure and robustness of these relationship(s) and the frequencies of the related mutations (as well as geographical and ethnic distributions) in order to understand the biological rationale...
behind this “inherited folate metabolism disorder” and have better management protocols (12, 14). MTHFR polymorphisms are more frequent than has been expected and caution should be exercised when drawing clinical conclusions (15-17).

This study set out to determine the prevalence of MTHFR (C677T and A1298C) homozygous polymorphism(s) in a specific population that necessitated MTHFR polymorphism investigation due to various reasons.

MATERIALS AND METHODS

This study consisted of 10449 patients who necessitated MTHFR polymorphism investigation owing to various reasons (CAD, thrombotic events, epilepsy, migraine, repeated miscarriages, various obstetric complications, etc.) during 2008-2017. Hacettepe University Hospital Electronic Registry was used for the retrieval of data. Our hospital is a referral center in the capital city of Turkey that provides multidisciplinary approach, and Ankara is located in Central Anatolia Region. The allelic frequencies of the mutations and the prevalence of homozygous MTHFR C677T and A1298C polymorphisms was determined. We have also analyzed the source of departments from where the laboratory tests were requested in between June 2008 and June 2012.

Data were analyzed using SPSS software program version 23. Qualitative data was presented as percentage and frequency, quantitative data was presented as mean ± standard deviation and number. The number of heterozygous and homozygous alleles (for both MTHFR 677 and 1298) were divided by the total number of alleles to calculate the allelic frequencies.

RESULTS

The prevalence of homozygous MTHFR C677T and A1298C polymorphisms are shown in Table 1. The prevalence of homozygous MTHFR C677T and A1298C polymorphisms were 10.3 and 11.3 respectively. Table 2 shows the allelic frequencies of MTHFR 677 and MTHFR 1298 mutations in the study group. The allelic frequencies for MTHFR 677 and MTHFR 1298 were 0.296 and 0.283 respectively.

Table 3 shows the origin of departments from where laboratory tests were requested. The data of 5205 patients in between June 2008 and June 2012 were used for this analysis (because of change at the electronic registry system of Hacettepe University Hospitals) and we have demonstrated that 38% of the cases were from obstetrics & gynecology (mainly obstetrics) and perinatology departments due to various reasons such as thrombotic events, bad obstetrical history (previous perinatal "morbidity/mortality", especially recurrent miscarriages) and various obstetric complications (during and after pregnancy).

Table 1: The Prevalence of Homozygous MTHFR C677T and A1298C Polymorphisms during 2008 to 2017 (htz: heterozygous, hom: homozygous, MTHFR: methylenetetrahydrofolate reductase)

<table>
<thead>
<tr>
<th>Year</th>
<th>677 hom</th>
<th>677 htz</th>
<th>1298 hom</th>
<th>1298 htz</th>
<th>677 htz/1298 htz</th>
<th>677 hom/1298 hom</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>141</td>
<td>58</td>
<td>136</td>
<td>62</td>
<td>91</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>2009</td>
<td>496</td>
<td>163</td>
<td>205</td>
<td>106</td>
<td>120</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>421</td>
<td>127</td>
<td>184</td>
<td>113</td>
<td>260</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>277</td>
<td>112</td>
<td>140</td>
<td>113</td>
<td>78</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>149</td>
<td>75</td>
<td>166</td>
<td>82</td>
<td>159</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>163</td>
<td>71</td>
<td>187</td>
<td>99</td>
<td>168</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>202</td>
<td>117</td>
<td>235</td>
<td>144</td>
<td>203</td>
<td>0</td>
<td>4</td>
<td>0</td>
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<tr>
<td>2015</td>
<td>254</td>
<td>141</td>
<td>315</td>
<td>201</td>
<td>264</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2016</td>
<td>246</td>
<td>145</td>
<td>301</td>
<td>179</td>
<td>107</td>
<td>4</td>
<td>3</td>
<td>0</td>
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<tr>
<td>2017</td>
<td>118</td>
<td>52</td>
<td>124</td>
<td>58</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2467</td>
<td>1061</td>
<td>1993</td>
<td>1157</td>
<td>1534</td>
<td>15</td>
<td>24</td>
<td>3</td>
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</tbody>
</table>

Table 2: Allelic frequencies of MTHFR 677 and MTHFR 1298 mutations in a population which is screened for vascular problems and/or thrombosis

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Allelic frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR 677</td>
<td>0.296</td>
</tr>
<tr>
<td>MTHFR 1298</td>
<td>0.283</td>
</tr>
</tbody>
</table>

Table 3: The origin of departments from where laboratory tests were requested
DISCUSSION

There are various reports related to the prevalence of MTHFR C677T and A1298C polymorphisms in different study populations in Turkey (18-23). Most of these studies are clinical series on different medical disorders (22, 24-26). In this short communication, we have aimed to demonstrate the allelic frequencies and the prevalence of homozygous MTHFR C677T and A1298C polymorphisms in patients that necessitated investigation of these mutations. The aim was to have a brief idea about the role and clinical importance of these two polymorphisms in high-risk patients in terms of biological events in combination with endothelial injury and folate metabolism disorders. In this study, we have shown that the allelic frequencies for MTHFR 677 and MTHFR 1298 were 0.296 and 0.283 respectively. It has been reported that allelic frequency of MTHFR C677T was 0.312 in a healthy Serbian population which was a little bit higher than our study population which was consisted of various risk factors, such as, vascular disorders, thrombotic events, folate metabolism disorders, genetic disorders, repeated miscarriages and obstetric complications (27).

The frequency of MTHFR polymorphisms was reported to vary in different ethnic groups. Studies among healthy populations in Greece, Japan, Lebanon and China, reported homozygous MTHFR C677T to be 17.8%, 11.5%, 11.0%, and 7.9%, respectively. However, the prevalence of homozygosity in the MTHFR A1298C genotype has not been as well studied as with C677T (28-31). In healthy Turkish populations, the prevalence of homozygosity were reported to vary between 8.8% and 9.6% for the C677T allele and 10% and 13.3% for the MTHFR A1298C allele (29, 32). Increased frequency of MTHFR polymorphisms was reported in patients with CAD, thrombotic events, epilepsy, migraine, repeated miscarriages and various obstetric complications (1-7). In our study, the prevalence of homozygous MTHFR C677T and A1298C polymorphisms were 10.2% and 11.1%, respectively, in a group of patients with various risk factors, namely, vascular disorders, thrombotic events, folate metabolism disorders, genetic disorders, repeated miscarriages and obstetric complications. Surprisingly, our findings are similar to the previous reports published from Turkey, although those studies were carried in healthy populations (18, 19, 22, 23). Thus, the prevalence of these polymorphisms in general Turkish population (may be with regional variations) should most probably be less than what we have demonstrated because our large study population is consisted of patients with various risk factors.

In this study, there were some limitations although it was informative and valuable in daily medical practice. First, study group was consisted of only the patients that necessitated MTHFR polymorphism investigation due to various risk factors in terms of thrombotic events. Second, we could not subclassify the patients in terms of coexisting medical disorders which may influence the results. Finally, it was not possible to claim that our findings indicate the entire Turkish population.

CONCLUSION

MTHFR polymorphisms are more than just risk factors for folate metabolism disorders and/or thrombotic events but triggers biological mechanisms for various medical/metabolic disorders.

REFERENCES


http://www.ejgm.co.uk