

THE ROLE OF THE METHYLENETETRAHYDROFOLATE REDUCTASE 677 C/T GENETIC POLYMORPHISM IN ETIOPATOGENY, CLINICAL PICTURE AND TREATMENT RESPONSE IN SCHIZOPHRENIA

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Abstract:

The 677 C/T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene was associated with schizophrenia in many studies.

Objective: To analyze the presence of the mutation in patients with schizophrenia and its influence on clinical feature and the responsiveness to treatment.

Material and method: 42 inpatients were psychiatrically and scalar evaluated. We performed DNA analysis of the 677C/T polymorphism of the MTHFR gene.

Results: The mutation was present in 28 (66.67%) of the patients compared to 12 (34.29%) of the control group ($p=0.005$). Patients with modified genotype had slightly higher mean scores in positive, negative and general symptoms. Patients with the mutation had a significant better response to atypical antipsychotics than patients with normal genotype ($p<0.002$).

Conclusions: Our study confirms the role of the MTHFR 677C/T polymorphism in the etiopathogeny of schizophrenia. The presence of T allele was associated to atypical antipsychotics response, but not to the intensity of symptoms.

Key words: schizophrenia, methylene-tetrahydrofolate-reductase (mthfr), atypical antipsychotics, treatment response, symptoms

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that catalyzes the conversion of 5,10 – methylenetetrahydrofolate to 5 – methyltetrahydrofolate, a methyl donor for the remethylation of homocysteine to methionine. The MTHFR gene lies on the 1p 36.3 region of the chromosome 1. A mutation of the gene in exon 5, position 677, which causes the substitution of C with

T, is responsible for the decrease in the activity of MTHFR, that results in hyperhomocysteinemia (1). Hyperhomocysteinemia has been associated with various diseases, including neural tube defects (2), vascular dementia (3), Alzheimer disease (4), cardio-vascular diseases (5) and cerebral vascular disease (6). Multiple studies have shown that the C/T mutation is related to schizophrenia (7-16), but other studies have failed to confirm it (17 – 21).

OBJECTIVE

To analyze the MTHFR 677C/T genetic polymorphism in 42 patients with schizophrenia. To evaluate the implication of the T allele in the etiopatogeny of schizophrenia and the possible influence on the clinical feature and the responsiveness to treatment.

MATERIAL AND METHODS

Forty two inpatients with schizophrenia committed in the “Socola” Psychiatry Hospital Iași, Romania, were included in the study. The patients signed an informed consent in order to participate.

The patients had been diagnosed with schizophrenia according to the International Classification of Diseases (ICD-10) criteria for a period of time of at least 3 years.

They were psychiatrically examined and evaluated with a modified PANSS scale which assessed every category of symptom with a score ranging from 1 (absent) to 7 (extreme). Seven questions evaluated the positive symptoms, 7 questions, the negative symptoms and 16 questions, the general symptoms. Data were obtained from attending doctors regarding evolution under medication.

A blood sample was obtained from the 42 patients and 35 controls. The DNA analysis was performed at the Molecular Biology Center, Institute for Experimental Interdisciplinary Research of the Babeș-Bolyai University in Cluj-Napoca, Romania, by PCR, restriction mapping and sequencing of the 677C/T genetic polymorphism in the MTHFR gene. All the individuals participating in this study were Caucasians of Romanian ancestry.

Statistical analysis was performed using the SPSS 13.0 package for Windows.

RESULTS

Of the 42 patients, 14 (33.3%) had the normal polymorphism (CC), 21 (50%) were heterozygotes (CT) and 7 (16.7%) were homozygotes for the abnormal allele (TT). The results of the control group were the following: 23 (65.71%) were CC homozygotes, 7 (20%) were heterozygotes and 5 (14.29%) were TT homozygotes. A significant difference ($\chi^2 = 8.01$, $df = 1$, $p = 0,005$) of the T allele distribution between patients and control subjects can be observed (Figure 1).

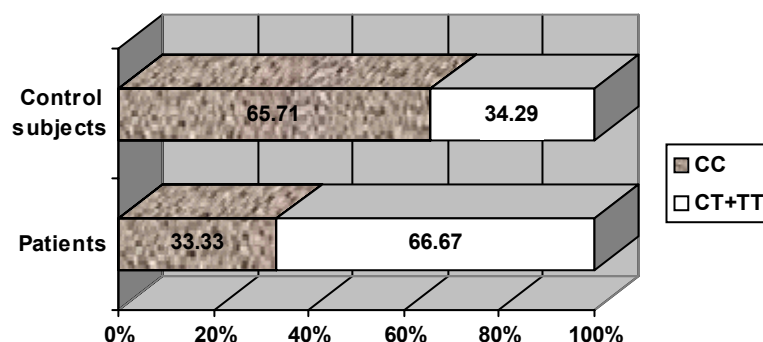


Fig. 1. Distribution (%) of the T mutation in the position 677 of the MTHFR gene among control subjects and patient group

The scalar evaluation revealed that the patients with modified genotype had slightly higher mean scores in all categories of symptoms (positive, negative and general) than patients having the normal variant of the MTHFR gene (Figure 2).

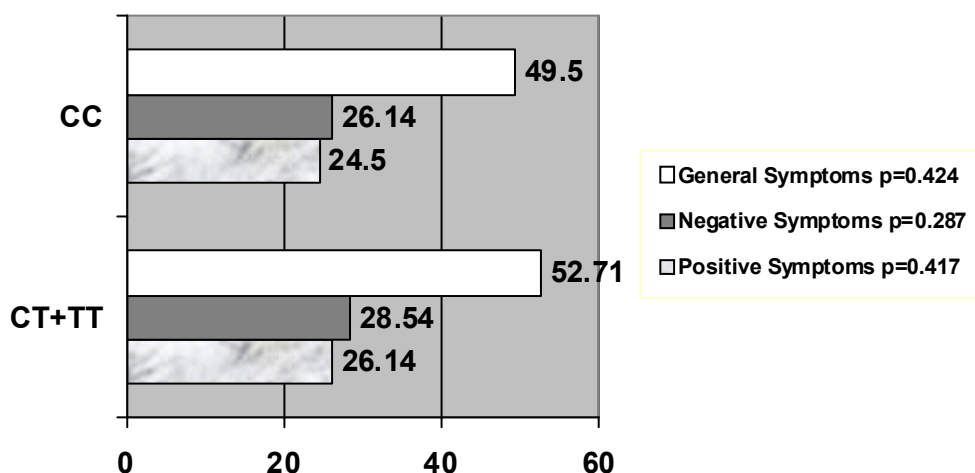


Fig. 2. Mean scores of the positive, negative and general symptoms in patients with modified genotype (CT+TT) and normal genotype (CC)

We assessed the medication to which the patients had a better outcome and response and we found that 28 (66.66%) patients responded to atypical antipsychotic treatment and 14 (33.34%) to typical antipsychotics. Data are resumed in Table 1.

Antipsychotic	CC Genotype	CT+TT Genotype
Olanzapine	2	4
Quetiapine	1	1
Aripiprazole	0	3
Ziprasidone	1	3
Risperidone	2	4
Clozapine	1	2
Amisulpride	0	5
Flupentixol	0	1
Haloperidol	7	3
Zuclopenthixol	1	1

Table I. Antipsychotic treatment in our group of patients

Of the 28 patients presenting the T allele, 22 (78.57 %) responded to atypical antipsychotics and only 6 (21.43%) to typical antipsychotics. The 14 patients with normal genotype responded to atypical antipsychotics in 7 cases (50%) and typical antipsychotics in 7 cases (50%). We observe that patients with the mutation had a significant ($\chi^2 = 9.14$, $DF = 1$, $p < 0.002$) better response to atypical antipsychotics, than the patients with normal genotype (Figure 3).

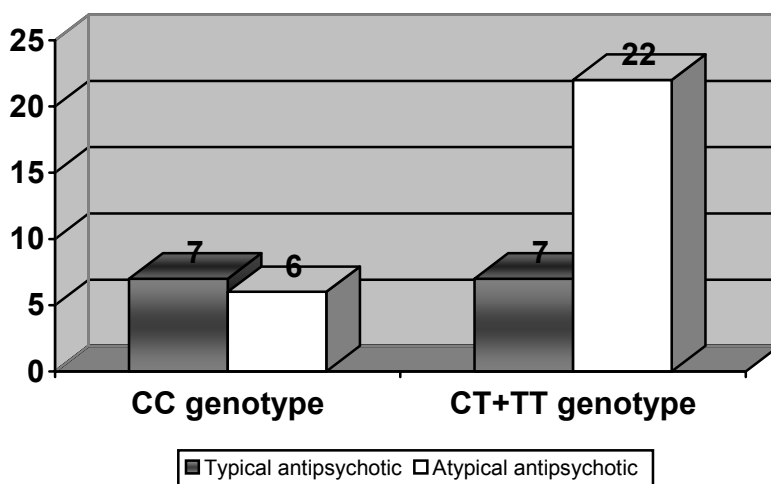


Fig. 3. *Type of antipsychotic treatment in patients with normal genotype (CC) and modified genotype (CT+TT)*

DISCUSSIONS

Our study confirms the initial study of Arinami and al (7) and the other subsequent studies (8 – 16) that the MTHFR 677T allele is associated to schizophrenia, although other studies (17 – 21) have failed to confirm it. The patient and controls were extremely homogenous regarding ethnicity (Romanian ancestry). Our results showed a strong association between the T allele and schizophrenia, which may reflect the implication of ethnicity rather than race in the genetic susceptibility to schizophrenia.

Schizophrenia is marked by positive and negative symptoms, characterized by psychotic episodes. The severity and regularity of these episodes vary from person to person (22). Roffman et al. (23) found that the 677T allele load was associated with negative symptom severity and protective against positive symptoms, in a sample of outpatients with schizophrenia. Our study revealed that patients presenting the mutation have increased severity of both negative and positive symptoms, but differences were not significant.

Joober et al. (8) reported that the MTHFR T allele is associated with a better response to antipsychotics and a better outcome. We found that patients with the T allele had a better response to atypical antipsychotics than patients with normal genotype.

CONCLUSIONS

1. Our study confirms the role of the MTHFR 677C/T polymorphism in the etiopathogenesis of schizophrenia.
2. The intensity of positive, negative and general symptoms was slightly increased in patients presenting the T allele.
3. The patients with the mutation had a better response to atypical antipsychotics than patients with normal genotype.

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