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Metabolic dysregulation in first-episode schizophrenia patients with respect to genetic variation in one-carbon metabolism

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ABSTRACT

The aim of this study was to investigate the prevalence of metabolic disturbances in patients with first-episode schizophrenia (FES) and test the hypothesis that genetic variation in one-carbon metabolism may account for metabolic dysregulation in early psychosis. We measured fasting glucose, lipid profile parameters, homocysteine, folate and vitamin B12 in 135 patients with FES and 146 healthy controls (HCs). Polymorphisms in the following genes were determined: *MTHFR* (C677T and A1298C), *MTHFD1* (G1958A), *MTRR* (A66G) and *BHMT* (G742A). Serum levels of folate and high-density lipoproteins (HDL) were significantly lower in patients with FES compared to HCs. In turn, serum levels of homocysteine and triglycerides were significantly higher in patients with FES than in HCs. Prevalence of hyperhomocysteinemia, low folate and HDL levels together with dyslipidemia was significantly higher in patients with FES compared to HCs. Higher homocysteine levels, lower vitamin B12 levels and the presence of metabolic syndrome were associated with higher severity of negative symptoms. None of studied polymorphisms was associated with schizophrenia risk. Several associations between studied polymorphisms and cardio-metabolic parameters were found. None of them remained significant after Bonferroni correction. Our results indicate that metabolic dysregulation in patients with FES is not associated with genetic variation in one-carbon metabolism.

1. Introduction

Life expectancy in patients with schizophrenia is reduced up to 20 years, mostly due to high prevalence of comorbid cardiovascular diseases (Laursen et al., 2011, 2013). A recent meta-analysis (Vancampfort et al., 2013) revealed that multi-episode schizophrenia patients are at increased risk for abdominal obesity, hypertension, hypertriglyceridemia, low levels of high-density lipoproteins (HDL), metabolic syndrome (MetS) and diabetes in comparison with the general population. In addition, it has been recognized that multi-episode schizophrenia patients have higher prevalence rates of these abnormalities, with exception of hypertension, than first-episode psychosis patients suggesting that aging and environmental factors play an important role in the development of cardiovascular diseases in patients with schizophrenia (Vancampfort et al., 2013). Indeed, several factors may underlie high prevalence of cardio-metabolic disturbances in this group of patients including adverse effects of pharmacological treatment (Hasnain et al., 2010; Foley and Morley, 2011), lifestyle characteristics such as low exercise activity (Vancampfort et al., 2011), poor dietary habits (Tsuruga et al., 2015) and cigarette smoking (de Leon and Diaz, 2005), as well as negative symptoms of schizophrenia (Sicras-Mainar et al., 2015).

Less is known about cardio-metabolic disturbances in first-episode patients and trajectories leading to unfavourable cardiovascular outcomes. It has been estimated that cigarette smoking, dyslipidemia and overweight are the most common cardiovascular risk factors in first-episode schizophrenia (FES) patients (Mitchell et al., 2013). There are also small studies showing higher levels of fasting glucose and insulin resistance (Ryan et al., 2003; Chen et al., 2013; Petrikis et al., 2015; Zhang et al., 2015), homocysteine (Hcy) (Kale et al., 2010; Ayesa-Arriola et al., 2012; Garcia-Bueno et al., 2013; Misiak et al., 2014b) as well as more pronounced lipid profile disturbances (Chen et al., 2013; Misiak et al., 2014b) in first-episode cases in comparison with healthy controls. However, some studies have not confirmed that first-episode psychosis patients

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are characterized by metabolic dysregulation (Graham et al., 2008; Sengupta et al., 2008; Verma et al., 2009; Foley and Morley, 2011; Phutane et al., 2011). Given that metabolic profile alterations have been reported in drug-naïve patients, it has been suggested that metabolic dysregulation in schizophrenia might be a consequence of common genetic underpinnings for psychotic and metabolic disorders (Ferentinos and Dikeos, 2012). In support of this hypothesis, there are studies showing that genetic polymorphisms in the following genes: *TCF7L2* (Irvin et al., 2009; Hansen et al., 2011), *AKT1* (Xu et al., 2007; Mathur et al., 2010) and *TSPAN8* (Scholz et al., 2010) might increase the risk of schizophrenia and diabetes.

Several meta-analyses have also reported that the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene is a risk factor for schizophrenia (Muntjewerff et al., 2006; Peerbooms et al., 2011; Nishi et al., 2014; Hu et al., 2015). However, negative results have been also published and genome-wide association studies (GWAS) have not confirmed these findings (Moustafa et al., 2014). More consistently, it has been found that the *MTHFR* C677T polymorphism may predict antipsychotic-induced weight gain in patients with schizophrenia (Srisawat et al., 2013; Kao et al., 2014). Importantly, the *MTHFR* C677T polymorphism might be a susceptibility gene for type 2 diabetes and its complications (Zhu et al., 2014; Zhou et al., 2015). This polymorphism is present in 10–12% of population and leads to the expression of thermolabile enzyme variant that may increase Hcy level (Gilbody et al., 2007). This polymorphism is associated with a decrease in enzymatic activity reaching 35–70% in homozygotes (Frosst et al., 1995). A non-protein amino acid Hcy is a known risk factor for atherosclerosis and may also play a role in the pathophysiology of schizophrenia in several mechanisms [for review see (Misiak et al., 2013; Moustafa et al., 2014)]. It has been also reported that elevated Hcy levels and genetic variation in enzymes involved in its metabolism might be associated with higher severity of negative symptoms (Roffman et al., 2013a).

Although the *MTHFR* gene polymorphisms (C677T and A1298C) have been widely investigated in patients with schizophrenia, a few research gaps in this field still exist. To date, there is a scarcity of studies looking at polymorphisms in other enzymes involved in Hcy metabolism in patients with schizophrenia. The *MTHFD1* gene encodes a protein that has three distinct enzymatic activities (methylenetetrahydrofolate dehydrogenase, methylenetetrahydrofolate cyclohydrolase and formyltetrahydrofolate synthetase) and is involved in the interconversion of one-carbon derivatives to tetrahydrofolate. A common *MTHFD1* polymorphism (G1958A) has been found to alter enzyme function and metabolic activity (Christensen et al., 2009). In turn, methionine synthase reductase (encoded by the *MTRR* gene) is required for reductive methylation of cobalamin, a process that activates methionine synthase (MTR) involved in the conversion of Hcy to methionine. It has been reported that the A66G polymorphism in the *MTRR* gene might have a functional impact on enzymatic activity since the *MTRR* 66AA homozygosity has been associated with moderate increase in Hcy levels (Gaughan et al., 2001). Finally, betaine-homocysteine methyltransferase (BHMT), another one-carbon metabolism enzyme, catalyses the transfer of a methyl group from betaine to Hcy leading to the synthesis of dimethylglycine and methionine. The G742A polymorphism in the *BHMT* gene has been found to alter enzyme kinetics (Li et al., 2008). Previous studies have not investigated functional polymorphisms in one-carbon metabolism genes with respect to a broad panel of metabolic parameters. Additionally, metabolic dysregulation in the early course of psychosis has not been studied with respect to genetic underpinnings. To bridge these gaps, we aimed to investigate whether functional polymorphisms in genes encoding enzymes involved in one-carbon metabolism (Fig. 1) including *MTHFR*, *MTHFD1*, *MTRR* and *BHMT* influence schizophrenia susceptibility and account for metabolic dysregulation reported in patients with FES. We also tested the relationship between polymorphisms in one-carbon metabolism, cardio-metabolic parameters and psychopathological manifestation of patients with FES.

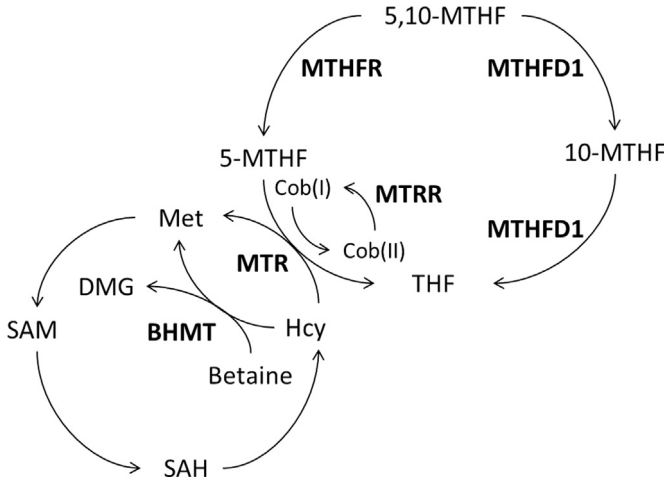

Fig. 1. Simplified scheme of one-carbon metabolism. *Abbreviations:* BHMT – betaine-homocysteine methyltransferase, Cob(I) – cobalamin with cobalt at the +1 oxidation state, Cob(II) – cobalamin with cobalt at the +2 oxidation state, DMG – dimethylglycine, Hcy – homocysteine, MTHFD1 – a trifunctional enzyme (methylenetetrahydrofolate dehydrogenase, methylenetetrahydrofolate cyclohydrolase and formyltetrahydrofolate synthetase), MTHF – methyltetrahydrofolate, MTHFR – methylenetetrahydrofolate reductase, MTR – methionine synthase, MTRR – methionine synthase reductase, SAH – S-adenosylhomocysteine, SAM – S-adenosylmethionine, THF – tetrahydrofolate.

2. Material and methods

2.1. Subjects

At baseline, 211 first-episode psychosis patients were consecutively admitted to Lower Silesian Centre of Mental Health (Wroclaw, Poland). Out of them, 76 patients were not recruited because they did not provide informed consent for participation in the study (22 patients) or did not meet the eligibility criteria (54 patients). Finally, 135 patients with FES of Caucasian ethnicity were recruited. In addition, 146 healthy controls (HCs) with negative family history of severe mental illness matched for age, gender and education were enrolled. A diagnosis of schizophrenia was based on ICD-10 and DSM-IV criteria. The Operational Criteria for Psychotic Illness (OPCRIT) checklist was used to validate a diagnosis. Duration of untreated psychosis (DUP) was defined as the time from appearance of first prodromal symptoms to initiation of antipsychotic treatment. Patients were excluded from the study if they met at least one of the following exclusion criteria: general brain disorder, mental retardation, positive urine screening for illicit drugs (amphetamine, cannabis, ecstasy or opiates), severe somatic comorbidities and drug and/or alcohol use disorder during one year prior to the onset of psychosis (with exception of nicotine dependence). Neither the patients nor HCs received supplementation of folic acid or B vitamins. The study was approved by the local Ethics Committee and all participants gave an informed consent. All procedures were performed in agreement with the Declaration of Helsinki.

Patients were treated with following antipsychotics: amisulpride (2 patients), haloperidol (20 patients), olanzapine (58 patients), quetiapine (1 patient) and risperidone (30 patients). There were 24 antipsychotic-naïve patients. Treatment duration was 6.1 ± 4.4 days (up to 17 days) and baseline chlorpromazine equivalent was 153.4 ± 111.4 mg/day. In addition, agitation and