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Increase in serum HDL level is associated with less negative symptoms after one year of antipsychotic treatment in first-episode psychosis

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ABSTRACT

Background: A potential link between increase in total cholesterol and triglycerides and clinical improvement has been observed during antipsychotic drug treatment in chronic schizophrenia patients, possibly due to drug related effects on lipid biosynthesis. We examined whether changes in serum lipids are associated with alleviation of psychosis symptoms after one year of antipsychotic drug treatment in a cohort of first-episode psychosis (FEP) patients.

Methods: A total of 132 non-affective antipsychotic-treated FEP patients were included through the Norwegian Thematically Organized Psychosis (TOP) project. Data on antipsychotic usage, serum lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG)), body mass index (BMI) and clinical state were obtained at baseline and after 12 months. The Positive and Negative Syndrome Scale (PANSS) was used to assess psychotic symptoms. Mixed-effects models were employed to examine the relationship between serum lipids and psychotic symptoms while controlling for potential confounders including BMI.

Results: An increase in HDL during one year of antipsychotic treatment was associated with reduction in PANSS negative subscores ($B = -0.48$, $p = 0.03$). This relationship was not affected by concurrent change in BMI (adjusted HDL: $B = -0.54$, $p = 0.02$). No significant associations were found between serum lipids, BMI and PANSS positive subscores.

Conclusion: We found that an increase in HDL level during antipsychotic treatment is associated with improvement in negative symptoms in FEP. These findings warrant further investigation to clarify the interaction between lipid pathways and psychosis.

1. Introduction

Metabolic disturbances such as obesity and dyslipidemia are common in schizophrenia (Allison et al., 1999; Mitchell et al., 2013; Vancampfort et al., 2013). These metabolic abnormalities may be caused by environmental factors, but can also be intrinsic to the illness itself (Mitchell et al., 2013; Vancampfort et al., 2013). Indeed, dyslipidemia has been observed in antipsychotic-naive and in first-episode psychosis (FEP) patients (Chen et al., 2013; De Hert et al., 2006; Enez Darcin et al., 2014; Fleischhacker et al., 2013; Kaddurah-Daouk et al., 2012; Misiak et al., 2016; Saari et al., 2004; Thakore, 2004; Verma et al., 2009; Wu et al., 2013; Zhai et al., 2017). In line with these findings, there is also evidence of overlapping genetic markers between disturbed lipid metabolism and schizophrenia (Andreassen et al., 2013). Additional findings of

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white matter abnormalities and reduced myelination in schizophrenia (Bernstein et al., 2015; Davis et al., 2016; Mighdoll et al., 2015) also indicate an involvement of lipids, as cholesterol is crucial for myelin formation and functioning (Dietschy and Turley, 2004; Saher et al., 2005; Verheijen et al., 2003).

The metabolic effects of many antipsychotic drugs further illuminate the possible link between lipid factors and schizophrenia. It is well known that treatment with antipsychotics may lead to weight gain and dyslipidemia (Goncalves et al., 2015; Musil et al., 2015; Young et al., 2015). Weight gain, mainly caused by enhanced appetite and food intake, may indirectly increase lipid levels, but it has also been shown that dyslipidemia can occur independently of weight gain in antipsychotic treated patients (Birkenaes et al., 2008; Lally et al., 2013; Procyshyn et al., 2007). Although antipsychotic-related metabolic changes have been associated with negative health consequences (De Hert et al., 2011; Mitchell et al., 2013; Nasrallah et al., 2015; Newcomer, 2005), there are also several studies that report a positive link between treatment-related weight gain and improvement in psychosis (Bai et al., 2006; Czobor et al., 2002; Gupta et al., 1999; Hermes et al., 2011; Lamberti et al., 1992; Lane et al., 2003; Leadbetter et al., 1992; Meltzer et al., 2003; Sharma et al., 2014). Similarly, treatment-related increases in serum triglycerides (TG) have been associated with improvement in overall psychotic symptoms, and with a reduction in positive symptoms (Atmaca et al., 2003; Lally et al., 2013; Pande et al., 2002). There are also reports of an association between an increase in TG and/or total cholesterol, and improvement in negative symptoms (Chen et al., 2014; Procyshyn et al., 2007) and in cognitive symptoms (Krakowski and Czobor, 2011). Recent advances in lipidomics research, moreover, have linked changes in cell membrane lipid profiles to treatment response, signifying the multifaceted role of lipids in psychosis (Kaddurah-Daouk et al., 2012; Tessier et al., 2016). Nevertheless, the nature of these associations is not fully clarified, as prior studies have mainly involved chronic patients in whom the long-term effect of poor lifestyle and multiple drug exposures may be difficult to disentangle.

The main objective of the present study was to explore the relationship between serum lipids and symptom relief in FEP patients during their first year of antipsychotic treatment. Our main hypothesis was that an increase in serum lipids during antipsychotic treatment would be associated with improvement of psychosis-related symptoms, even after controlling for potential confounders including changes in body mass index (BMI). To test our hypothesis, we used data from a longitudinal sample of FEP patients where data regarding serum lipids, BMI and clinical state (i.e. positive and negative symptoms) at baseline and after 12 months of treatment were obtained.

2. Materials and methods

2.1. Study design

The present study is a prospective longitudinal study with a naturalistic design, with patients recruited at their first treatment for a psychotic disorder from inpatient and outpatient psychiatric units in the catchment areas of the major hospitals in Oslo, Norway, as part of the larger Thematically Organized Psychosis (TOP) study (http://www.med.uio.no/norment/english/). The Regional Ethics Committee and The Norwegian Data Inspectorate approved the study.

2.2. Patients

One hundred and thirty-two FEP patients were included in the present study (see Fig. 1). The inclusion criteria followed the general inclusion criteria for the TOP study: (1) age 18 to 65 years, (2) meeting the diagnostic criteria for a broad schizophrenia spectrum psychosis according to Diagnostic and Structural Manual of Mental Disorders, fourth version (DSM-IV, American Psychiatric Association, 2000), (3) no head trauma, neurological or other medical disorder that could influence CNS functioning, and (4) IQ over 70. The specific inclusion criteria for this longitudinal study was that the patient had not previously received adequate treatment for their psychotic disorder. Adequate treatment was defined as antipsychotic medication in doses over 1 Defined Daily Dosage (DDD) for >12 weeks or shorter if this treatment was followed by symptomatic remission; "first episode psychosis". DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/ddd/definition_and_general_considera/). In general, the patients were recruited in the early phases of treatment. However, some individuals were too psychotic to give informed consent at an early stage and patients could thus give consent to enter the study up to 52 weeks after start of first treatment (for details see Simonsen et al., 2017). For the purposes of the analyses in the current paper we did not include patients who (1) were not using any antipsychotics at baseline as well as at follow-up, and (2) participants treated with cholesterol-lowering medications (statins and fibrates).

The distribution of diagnoses was as follows: $N = 87$ (66%) with a diagnosis of schizophrenia, $N = 5$ (4%) schizophreniform disorder, $N = 16$ (12%) schizoaffective disorder and $N = 24$ (18%) psychotic disorder not otherwise specified (psychosis NOS).

2.3. Clinical assessments

Sociodemographic history (including age, gender, ethnicity, education), smoking, alcohol consumption, diet, exercise habits, duration of untreated psychosis (DUP), hospitalization, antipsychotic medication, and use of cholesterol-lowering medication were obtained through structured interviews. The ethnicity of patients was categorized as Caucasian or non-Caucasian. All patients were diagnosed with the Structural Clinical Interview for DSM-IV (SCID) (First et al., 1996). Inter-rater reliability was good, with an overall kappa score of 0.77 (95% CI: 0.60–0.94). Psychotic and other related symptoms were assessed using The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), we report the means for a five-factor model (Wallwork et al., 2012). Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). The extent of alcohol use was measured with The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Diet and exercise habits were assessed at inclusion and at 12 months by interviews. The patients were asked to describe their eating habits as healthy, moderately healthy or unhealthy. This variable was then dichotomized into "similar or poorer diet" (including patients who did not change their diet habits from inclusion to 12 months, as well as patients who reported a poorer diet at 12 months) and "better diet" (consisting of patients who reported a beneficial change in diet). Exercise was also initially assessed as light, moderate or hard, and then dichotomized into "similar or reduced exercise" and "increased exercise" at 12 months. Our rationale for dichotomizing diet and exercise was that we were primarily interested in the change in these variables, as they would reflect improvement or decline in lifestyle.

2.4. Use of antipsychotic medication

Information about current and previous use of antipsychotics was obtained through interviews with the patients combined with prescription data from the medical charts. All participants used one or more antipsychotics at least once during the study period (see Supplementary Tables 1–4, for information concerning antipsychotic and non-psychotropic drug use). For the purpose of this study, where our main goal was to investigate if serum lipid changes during antipsychotic drug therapy were related to improvement in psychosis, we defined treatment with any type of antipsychotic agent throughout the study period as continuous antipsychotic use ($n = 100$; 76%). In contrast, treatment

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