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Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis

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ABSTRACT

Background: Metabolic abnormalities and peripheral inflammation have been increasingly reported in patients at the onset of psychosis and associated with important physical health disorders and increased mortality. However, the impact of an abnormal metabolic-inflammatory status on the psychiatric outcome of these patients has not yet been investigated.

Objectives: The aims of this study were 1) to explore whether, in a sample of patients at their first episode of psychosis (FEP), an overall metabolic-inflammatory status may be measured, by combining metabolic and inflammatory variables in metabolic-inflammatory factors; 2) to explore the association between these factors and clinical outcome at 1-year follow-up (FU), in terms of symptoms severity and treatment response.

Methods: In this longitudinal study we recruited 42 FEP patients and 46 healthy controls (HC) matched with patients for age, gender and ethnicity. At baseline (T1) we measured high sensitivity C-reactive protein (hsCRP) as biomarker of inflammation, and body mass index (BMI), lipid profile and gluco-metabolic parameters (glycated hemoglobin (HbA1c) and fasting glucose) as metabolic variables. A principal component analysis (PCA) was then used to reduce the dimensionality of the dataset accounting for both inflammation and metabolic status. In FEP patients, we assessed symptoms severity at T1 and at 1-year FU (T2) as well as treatment response to antipsychotics at T2.

Results: at T1, FEP showed higher HbA1c ($p = 0.034$), triglycerides (TG) ($p = 0.045$) and BMI ($p = 0.026$) than HC. PCA identified 3 factors: factor 1 accounting for hsCRP, TG and BMI, factor 2 accounting for LDL and cholesterol, and factor 3 accounting for fasting glucose and HbA1c. Factor 1 was associated with T1 negative symptoms severity ($p = 0.021$) and predicted T2 positive ($p = 0.004$) and overall symptoms severity (0.001), as well as general psychopathology ($p < 0.001$) and T2 treatment response ($p = 0.007$).

Conclusion: In this sample of FEP patients, inflammation and metabolism, closely correlated at the onset of psychosis, proved to play a key role as predictors of the clinical course of psychosis when combined in a single factor. These findings offer an important potential target for early screening and interventions.

1. Introduction

Metabolic abnormalities and peripheral inflammation have been increasingly reported in patients with psychosis, often already at illness onset (Hepgul et al., 2012; Pillinger et al., 2017b; Russell et al., 2015). The combination of overweight, dyslipidaemia, hyperglycaemia and

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peripheral immune activation can lead to severe cardiovascular diseases, like metabolic syndrome, and to increased mortality in patients with psychosis (Leonard et al., 2012; Ringen et al., 2014). However, the consequences of this abnormal metabolic-inflammatory state for the psychiatric/mental health clinical outcome in patients at the onset of psychosis remain undetermined.

Recent evidence from our group has shown that increased baseline peripheral inflammatory markers, such as interleukin (IL)-6, predict poor treatment response at 3-month follow-up in patients with first episode psychosis (FEP) (Mondelli et al., 2015). Similarly, metabolic abnormalities in patients with bipolar disorder have been reported to be associated with worse psychiatric clinical outcome, including higher number of relapses, hospitalizations and more impaired cognitive functioning (Bai et al., 2016; Calkin et al., 2009; Fagiolini et al., 2003). Some emerging evidence on the effects of inflammation and metabolic abnormalities on the brain can possibly explain this association. For example, treatment with IL-1β, a pro-inflammatory cytokine shown to be increased in patients with depression or with schizophrenia, decreases neurogenesis in human hippocampal progenitor cells (Zunszain et al., 2012). Further evidence of the effect of metabolism on the brain comes from resting-state studies. A study from Doucet et al. (2018) investigated the correlation between BMI and the functional organization of resting-state brain networks, such as the default mode network (DMN), and the Sensory Motor Network (SMN). They found a positive correlation between BMI and connectivity between the DMN, the SMN and other cerebral networks. Such increased integration between networks suggests an increase of sensory driven behavior in subjects with higher BMI (Doucet et al., 2018). More interestingly, FEP patients show similar connectivity alterations. Resting-state studies have found that the early stage of schizophrenia is associated with increased connectivity between fronto-parietal networks involved in the control of cognitive and sensory functions (Anhoj et al., 2018).

Finally, obesity and overweight are associated with brain structural abnormalities (frontal and temporal grey matter atrophy and reduced integrity of white matter in the corpus callosum) and poor cognitive and functional outcomes, typically present in FEP (Minichino et al., 2017).

Growing evidence suggests increased levels of peripheral immune markers in patients at the onset of psychosis (Di Nicola et al., 2013; Hepgul et al., 2012; Mondelli et al., 2015; Zajkowska and Mondelli, 2014), and the potential for biomarkers of inflammation as predictors of long-term illness course (Mondelli et al., 2015). Similarly, levels of the acute phase inflammatory marker C-reactive protein (CRP) have been found moderately increased in patients with schizophrenia (Wang et al., 2017) and resulted to be correlated with the severity of illness and with the presence of relapses (Orsolini et al., 2018). Furthermore, in both chronic schizophrenia and at the onset of psychosis, CRP blood levels have been correlated with cognitive and negative symptoms severity (Baumeister et al., 2014). Despite such evidence, longitudinal studies investigating CRP as a predictor of clinical outcome at the onset of psychosis are currently lacking.

A further aspect to consider is that, due to the relationship between the immune and the metabolic system, high levels of peripheral inflammation are generally associated with metabolic abnormalities in both the general population and in FEP patients (Russell et al., 2015) (Petrikis et al., 2015; Pillinger et al., 2017a, b; Chen et al., 2013). More interestingly, weight gain, increased visceral fat and impaired glucose metabolism have been detected also in drug naïve patients (Correll et al., 2014), with altered insulin signaling being present also in unaffected siblings (Chouinard et al., 2018). This suggests these abnormalities to be partly independent of treatment exposure and rather to be linked to innate mechanisms of psychiatric illness, including a chronic inflammation state.

All this evidence supports the relevance of considering an overall metabolic-inflammatory status when looking for biomarkers of clinical outcomes of psychosis. No study so far has tested the impact of the combination of inflammation-weight gain-metabolic abnormalities on the clinical outcome of FEP patients. Based on this evidence, this study aimed to investigate whether, in a sample of FEP patients, inflammation and metabolic status could be considered together as part of an overall inflammatory-metabolic factor associated with clinical symptoms at baseline and at 1-year follow-up clinical outcome. There is a compelling body of evidence on the association between inflammation and BMI and adiposity. In fact, obese individuals present higher circulating levels of CRP (Firdous, 2014); in particular, it is now acknowledged that adipose tissue can contribute to increased peripheral inflammation due to the increased release of cytokines from adipocytes and infiltrated macrophages (Wensveen et al., 2015).

As a consequence, we hypothesized that a single factor representing a latent metabolic process variable between individuals would express a linear combination of baseline inflammation, BMI and/or adiposity and that it could be positively associated with symptoms severity at baseline and with 1-year follow-up symptoms severity and treatment response.

2. Materials and methods

This is a naturalistic longitudinal study in which FEP patients were assessed at baseline (i.e., as soon as possible and within 3 months after the first contact with psychiatric services) and then were followed-up prospectively for their clinical outcome at 1 year.

2.1. Sample and study design

2.1.1. First episode psychosis patients

Fifty-one first episode psychosis patients were recruited in South-East London as part of the Physical health and substance Use Measures in first onset Psychosis (PUMP) and Genetics and Psychosis (GAP) studies. The recruitment strategy was based on contacting inpatient and outpatient units of the South London and Maudsley (SLAM) NHS Foundation Trust, interviewing staff and reviewing clinical notes, and approaching all subjects aged 18–65 who presented for the first time to these services for a functional psychotic illness. Patients not fluent in English, with organic psychosis, learning disabilities, mental retardation, and physical comorbidities affecting the immune system (acute and chronic infections, auto-immune disorders, diabetes and cardiovascular disorders) were excluded from the study. Two patients were not included as they had an acute infection and a history of chronic inflammation due to an autoimmune disorder, respectively; seven patients with diabetes, of which six were on insulin treatment, were also excluded. The final sample was of 42 FEP patients. All patients were assessed as soon as possible after their first contact with psychiatric services, and not later than 3 months from the first contact. After 1 year, a clinical follow-up was completed on all patients to establish treatment response and illness course. The study was approved by the local Research Ethics Committee, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained from all participants.

At the time of the first assessment, 20 patients were taking olanzapine, 13 were taking risperidone, 4 were taking quetiapine, 3 were taking aripiprazole, 1 was taking haloperidol and 1 was taking zuclopenthixole. Total duration of treatment from baseline (T1) to follow-up (T2) was calculated, as well as total treatment duration at T1 and the main duration of untreated psychosis. Unfortunately, information about the main duration of untreated psychosis was available for 34 patients only. According to published guidelines (Gardner et al., 2010), chlorpromazine equivalents of the cumulative dosage of medications at T1 and T2 were calculated.

Twenty-one patients received a DSM-IV diagnosis of schizophrenia/schizophreniform disorder, 17 of schizoaffective or affective psychosis and 4 of psychotic disorder not otherwise specified. Validation of clinical diagnosis was obtained using the Operational Criteria (OPCRIT+), reviewing the case notes in the first month following first contact with services. All diagnoses were performed by qualified psychiatrists, subject

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