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METABOLIC PARAMETERS AS POSSIBLE DIAGNOSTIC PREDICTORS IN FIRST-EPIISODE PSYCHOSIS: AN EXPLORATORY RETROSPECTIVE COHORT STUDY

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Keywords:	first-episode psychosis, mood disorders, schizophrenia, uric acid

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4 **FIRST-EPIISODE PSYCHOSIS: AN EXPLORATORY RETROSPECTIVE COHORT**
5 **STUDY**
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ABSTRACT

Aim: Patients in early phases of schizophrenia or mood disorders with psychotic symptoms have a wide array of metabolic abnormalities. We analysed the potential predictive value of uric acid levels and other metabolic parameters in first-episode psychosis patients to differentiate between non-affective and affective psychosis.

Methods: Retrospective chart review of patients referenced to a first-episode psychosis unit between 2012-2017 with available uric acid levels. Patients included (n=37) were compared according to the follow-up diagnosis of schizophrenia or mood disorder.

Results: Mood disorder patients presented higher uric acid levels ($p=0.030$) and lower fasting blood glucose levels ($p=0.020$) compared with schizophrenia patients. Remaining variables did not show significant intergroup differences.

Conclusions: Findings in this first-episode psychosis cohort support previous evidence suggesting higher uric acid levels as predictor of affective psychosis and glucose dysfunction as predictor of schizophrenia. Further studies are needed to explore metabolic parameters as possible diagnostic predictor in first-episode psychosis.

KEYWORDS

Early intervention, first-episode psychosis, mood disorders, schizophrenia, uric acid

INTRODUCTION

Serious mental disorders are associated with substantial premature mortality and morbidity resulting of various contributing factors, including cardiovascular disorders and metabolic complications (Hayes et al., 2015; Hjorthøj et al., 2017). Metabolic abnormalities have been extensively described in patients with schizophrenia (SCZ) and mood disorders (MD), and were found in several disease stages, under different medical treatments, and even in drug-naïve patients (Bartoli et al., 2017; Fusar-Poli et al., 2021; Machado-Vieira et al., 2017; Malewska-Kasprzak et al., 2019; Oliveira et al., 2019; Pillinger et al., 2017; Salvatore et al., 2010; Steiner et al., 2014; Yang et al., 2013; Zhang et al., 2015). To reduce disease burden and impairment, earlier identification and enhanced care of those who are in the early phases of these mental disorders have been prioritized.

Nonetheless, there are no well-established biomarkers to predict the risk of conversion to SCZ or affective psychosis - bipolar disorder (BD) or schizoaffective disorder (SZA) - in patients with first-episode psychosis (FEP). Although several candidate peripheral biomarkers have been proposed for BD (Britzke et al., 2016) and for SCZ (e.g., BDNF, IL-2, TNF, or pentosidine), these parameters are mostly unavailable in routine clinical practice (Lai et al., 2016).

For BD, although reliable peripheral blood biomarkers are unavailable, we reported, in a recent study, that serum uric acid (UA) levels in inpatients with major depressive disorder (MDD) had excellent prognostic accuracy as a biomarker of conversion to BD (Oliveira et al., 2019), with independent studies supporting this finding (Meng et al., 2020; Kim et al., 2020). The purinergic system plays a role in regulating many physiological processes, namely mood, and robust evidence supports its relevance in the pathogenesis of BD (Pillinger et al., 2017). Previous studies also suggest a high prevalence of lipid and glucose abnormalities in patients with SCZ and MD (Fusar-Poli et al., 2021; Wysokiński et al., 2015); additionally, recent meta-analyses have demonstrated an association between SCZ and early derangements in glucose homeostasis (Pillinger et al., 2017; Yang et al., 2020).

Supported in available data, we hypothesized if UA levels and other metabolic parameters in FEP patients could be predictors of subsequent evolution to SCZ or MD.

METHODS

Participants

A retrospective chart survey was made of all patients referenced to the FEP unit of a large tertiary hospital between 2012 and 2017 (n=149). Inclusion criteria comprised: (1) UA levels available at admission; (2) an established diagnosis, according to International Classification of Diseases, 10th Revision (ICD-10), after a follow-up period of at least 2 years, of SCZ or MD (BD or SZA). Defined exclusion criteria were: known UA pathology (such as gout); use of UA interfering medication (such as allopurinol); **alcohol abuse or dependence**. A total of 37 participants had available UA levels at referral, fulfilling all inclusion and exclusion criteria: 26 had a follow-up diagnosis of SCZ, and 11 were diagnosed with MD (BP: n=9; SCZ: n=22).

Assessment

We conducted a retrospective review of patient records, assessing sociodemographic data, antipsychotic medication at admission normalized to defined daily dose (DDD), UA levels at admission and other metabolic parameters available (fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides).

Statistical Analysis

Statistical processing of data was performed using SPSS version 25 (IBM, Armonk, NY). Normality tests (Shapiro-Wilk test) were done for each variable under study; measures of central tendency and measures of spread were decided accordingly.

Pearson's chi-square test was applied to compare the distribution of patients by sex; Mann-Whitney U test was performed to compare antipsychotic medication and age between the two groups - SCZ vs. MD. A statistically significant difference was considered when a p-value below 0.05 was obtained.

Logistic regression was the selected analysis method for the different metabolic parameters, using SCZ vs. MD as dependent variable.

RESULTS

Descriptive and inferential statistics are presented in **Table 1**. Patients with a follow-up diagnosis of MD presented higher UA levels and lower levels of fasting blood glucose compared to individuals diagnosed with SCZ. Other analyzed variables did not show significant differences between groups. Data supporting this study are available from the corresponding author upon reasonable request.

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DISCUSSION

Our results were in line with previous studies concerning the purinergic system in MD (Bartoli et al., 2017; Machado-Vieira et al., 2017; Malewska-Kasprzak et al., 2019; Oliveira et al., 2019; Salvadore et al., 2010) and glucose metabolism dysfunction in SCZ patients (Pillinger et al., 2017; Steiner et al., 2014; Yang et al., 2013; Zhang et al., 2015). Additional metabolic parameters analyzed in this study, namely lipid levels, did not show statistically significant differences between groups.

Discussion on the relationship between BD and UA goes back to the 19th century, and increasing data suggest that purinergic system impairment plays a part in the pathophysiology of MD (Oliveira et al., 2019). Increased UA levels are associated with accelerated purinergic transformation and decreased adenosinergic transmission; it has been hypothesized that reduced adenosinergic activity (with a corresponding increase in UA levels) is associated with the complex dysfunction on neurotransmitters' pathways related to manic behavior (Oliveira et al., 2019). Furthermore, allopurinol (a hypouricemic agent) has been shown to be effective in treating acute mania when used together with a mood stabilizer (Oliveira et al., 2019).

A recent systematic review and meta-analysis found that patients with SCZ had increased fasting plasma glucose, reduced glucose tolerance, raised fasting plasma insulin and insulin resistance at illness onset; restricting the analysis to diet/exercise matched samples, significance was maintained for raised fasting glucose in patients (Pillinger et al., 2017). These findings show glucose homeostasis is altered from illness onset in SCZ (Nosè et al., 2008; Yang et al., 2020), which might have several possible explanations. Both SCZ and type 2 diabetes mellitus are associated with early developmental risk factors; stress and hypercortisolemia may also contribute to this association between both conditions, and there is also evidence for a shared genetic vulnerability (Pillinger et al., 2017).

As widely recognized, antipsychotic drugs have potential metabolic side effects, and medicated patients may present associated anomalies. The DDD system, a reliable tool for standardizing antipsychotic doses in drug research (Nosè et al., 2008), was used for comparison purposes. Antipsychotic medications were apparently unrelated to the metabolic changes found.

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3 FEP patients with a follow-up diagnosis of MD presented higher UA levels; therefore,
4 higher UA levels may prove helpful as a potential biomarker to predict conversion risk
5 to MD in this specific population. On the other hand, glycaemic dysfunction is
6 apparently more characteristic of non-affective psychosis, as the FEP patient group
7 with a follow-up diagnosis of SCZ presented higher levels of fasting blood glucose.
8 Thus, higher levels of fasting blood glucose might help to predict FEP patients' risk of
9 conversion to SCZ. Our hypothesis for the metabolic parameters as diagnostic
10 predictors in FEP psychosis is summarized in **Figure 1**.
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17 Disruptions of UA and glucidic metabolism of FEP patients (Kucukgoncu et al., 2019;
18 Pillinger et al., 2017; Reddy et al., 2003) are an innovative and clinically relevant
19 research pathway. The use of simple laboratory biomarkers combined with clinical
20 features might reduce the delay between onset and diagnosis, with treatment and
21 prognostic implications.
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26 This work had some limitations - a small sample size, its retrospective design, and
27 imbalance between groups. Our selection criteria, although essential for quality
28 purposes, excluded a considerable number of patients. Nevertheless, the results
29 obtained are in line with recent studies in this area. Additional studies, longitudinal and
30 preferably multicentric, prospectively following FEP cohorts, are of utmost importance.
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CONFLICT OF INTEREST STATEMENT

NM has been a consultant or advisory board member to Angelini, AstraZeneca, Ferrer, and Janssen. VS has been an advisory board member to Janssen. All other authors have no conflicts of interest to report.

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TABLES

TABLE 1 – Descriptive and inferential statistics

Demographic and clinical parameters	SCZ (M ± SD / IQR)	MD (M ± SD / IQR)	p-value
Sex (♂;♀)	21; 5	7; 4	0.267 [†]
Age (years)	25 ± 6	22 ± 14	0.566 [§]
Antipsychotics (DDD)	1.00 ± 1.14	0.60 ± 1.80	0.332 [§]
Uric acid levels (mg/dL)	5.38 ± 0.18	6.32 ± 0.47	0.030 ^{* †}
Fasting Blood Glucose (mg/dL)	84.00 ± 13.25	79.00 ± 8.00	0.020 ^{* †}
Total Cholesterol (mg/dL)	159.50 ± 54.25	152.00 ± 53.00	0.357 [‡]
LDL Cholesterol (mg/dL)	98.26 ± 6.37	79.09 ± 7.69	0.079 [‡]
HDL Cholesterol (mg/dL)	47.27 ± 2.24	55.73 ± 4.20	0.059 [‡]
Triglycerides (mg/dL)	91.00 ± 71.25	71.00 ± 132.00	0.836 [‡]

Abbreviations: DDD, defined daily dose; M ± SD / IQR, mean ± standard deviation or median ± interquartile range; MD, mood disorder; SCZ, schizophrenia

Note: † = Pearson's chi-squared test; ‡ = Mann-Whitney U test; § = Logistic Regression;
* p-value < 0.05

FIGURES

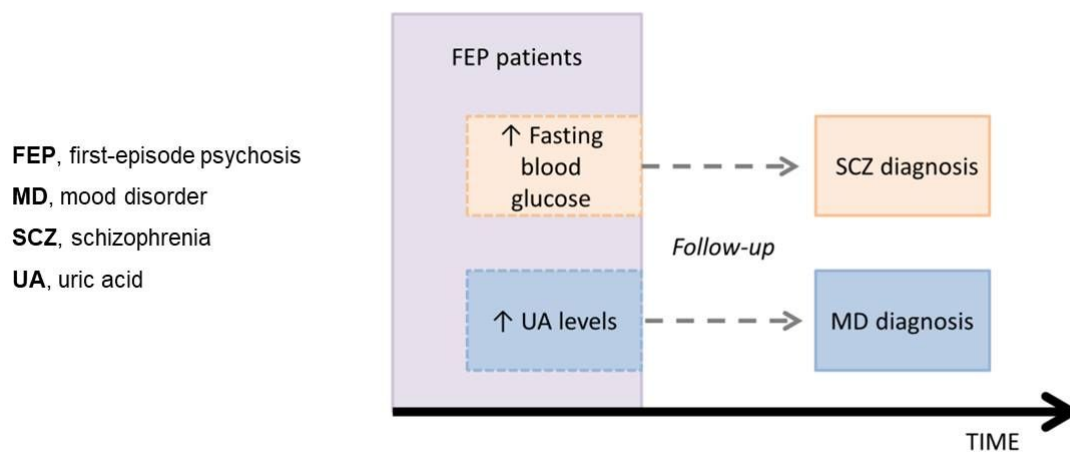
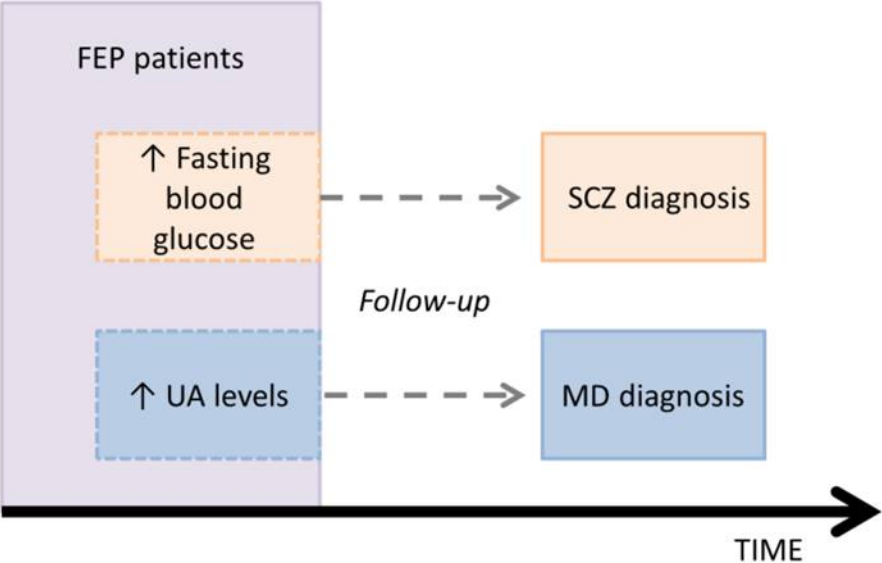


FIGURE 1 – Hypothesis for metabolic parameters as diagnostic predictors in first-episode psychosis

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5 **FEP**, first-episode psychosis
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7 **MD**, mood disorder
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9 **SCZ**, schizophrenia
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11 **UA**, uric acid



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