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Routine cerebrospinal fluid parameters as biomarkers in first-episode psychosis: A prospective observational study

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ABSTRACT

In recent years, multiple studies have investigated the role of biomarkers in first-episode psychosis (FEP) to facilitate early diagnosis, disease stratification, therapeutic choice and outcome prediction. Few studies have focused on cerebrospinal fluid (CSF) investigations. In this prospective observational study, 95 FEP inpatients were followed up for one year. A lumbar puncture was performed at index admission (baseline) to study the CSF parameters (glucose, total proteins, lactate dehydrogenase [LDH], and pleocytosis). At the baseline visit, the clinical assessment included prodromal (psychotic and non-psychotic) symptoms before the psychotic outbreak and psychopathology at admission. The SCID-I was administered to obtain a clinical diagnosis at baseline and at 12 months. The relationship between prodromal and psychopathology symptoms at the baseline visit was tested with multiple linear regression. Multinomial logistic regression was also used to explore the association between CSF biomarkers and longitudinal diagnoses at follow-up (schizophrenia/schizoaffective disorder vs unipolar/bipolar depression vs other psychoses). Higher CSF glucose was associated with depressive (Standardized beta = 0.27, $p = 0.041$) and disorganized/concrete symptoms (Standardized beta = 0.33, $p = 0.023$) and lower CSF LDH was associated with prodromal symptoms (Standardized beta = −0.25, $p = 0.042$). Lower LDH concentrations were also associated with social withdrawal ($r = -0.342$, $p = 0.001$). CSF glucose was a predictor of the long-term diagnosis (lower CSF concentrations were associated with schizophrenia or schizoaffective disorder diagnoses [OR = 0.88, CI95%: 0.77–0.99). Our study suggests that CSF biomarkers that involve bioenergetic systems are associated with prodromal symptoms and the phenotype of psychotic disorders during the early stages of the disease.

1. Introduction

First-episode psychosis (FEP) refers to the symptomatic emergence of myriad disorders, such as schizophrenia, schizoaffective disorder or bipolar disorder. These disorders are usually preceded by a prodromal phase, typically lasting months or years, in which subtle symptoms appear and are associated with reductions in functioning in several areas, including socio-familiar relationships and academic and occupational performance (Woodberry et al., 2016). The prodromal phase is a complex phenomenon during which attenuated psychotic symptoms, negative symptoms, cognitive alterations, depressive and anxiety symptoms, or changes in conduct can appear (Woodberry et al., 2016). This prodromal phase has been associated with poor functioning, and the duration of untreated psychosis (DUP) and the duration of untreated illness (DUI), as well as most cognitive variables (cognitive ability, attention, processing speed, verbal fluency, verbal memory and working memory), are consistently related to functional recovery in patients with FEP (Santesteban-Echarri et al., 2017). It is important to note that

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although attenuated psychotic symptoms during the prodromal phase have been linked to poor functioning (Rosengard et al., 2019), nonpsychotic symptoms (including negative symptoms) are more frequently the first prodromal symptoms (Cupo et al., 2021) and are also associated with poor functioning in longitudinal studies (Burton et al., 2019). Unfortunately, there are no effective treatments for improving negative symptoms in people with schizophrenia (Fusar-Poli et al., 2015). Research on new therapeutic targets of negative symptoms is crucial for improving the prognosis of schizophrenia and other psychotic disorders.

The aetiology and pathogenesis of psychosis are not yet fully understood, although the weight of evidence suggests a contribution from both genetic and environmental factors (Brown, 2011; Tsuang et al., 2004). The lack of biomarkers contributes to diagnostic delay and hinders disease stratification, therapeutic choice and prediction of outcomes (Weickert et al., 2013). Accumulated evidence has implicated inflammation and the immune system in the aetiology of psychosis (Kodavali et al., 2014; Najjar and Pearlman, 2015), suggesting that biological markers might emerge from a better understanding of the involvement of these systems in psychotic disorders.

Only a few studies have focused on cerebrospinal fluid (CSF) investigations. CSF is a dynamic, metabolically active secretion that can provide important information pertaining to inflammatory changes involving the brain (Deisenhammer et al., 2006). In a recent systematic review and meta-analysis on CSF markers of inflammation in schizophrenia and affective disorders, increased albumin ratios and total protein suggestive of blood-brain-barrier (BBB) leakage or dysfunction were the major findings (Orlovska-Waast et al., 2019). As some types of autoimmune encephalitis (e.g., anti-N-methyl D-aspartate receptor antibodies [NMDAR-Abs]) might present with psychotic symptoms (Giné Servén et al., 2021), previous studies have examined the hypothesis of whether a subgroup of psychotic syndromes might have an underlying autoimmune process, mainly searching for NMDAR antibodies in serum, with inconsistent results (Cullen et al., 2021). These studies are difficult to interpret because none of them has systematically examined both the serum and the CSF (e.g., combining brain immunohistochemistry, cell-based assay, and live neurons) to minimize false results or to disregard antibodies of limited specificity. To solve this limitation, our group carried out a prospective study in which CSF and serum for neuronal antibodies were examined in a sample of 105 FEP patients using three different techniques, and we failed to discover any positive cases of glutamic acid decarboxylase 65-kilodalton isoform antibodies (GAD65-Abs) or NMDAR-Abs (Guasp et al., 2021).

However, few studies have explored the relationship between the clinical expression of psychotic disorders and inflammatory markers. Some studies conducted several decades ago in patients with schizophrenia reported an association between CSF alterations (increased permeability of the BBB with an elevated albumin CSF/serum quotient and increased IgG in the CSF) and negative symptoms (Müller, 1995). Nevertheless, as reported in a recent meta-analysis, most studies that have explored the association between CSF metabolites (including total protein or cytokines) and symptoms in patients with schizophrenia have been negative (Orlovska-Waast et al., 2019). The majority of these studies have been conducted in patients with chronic schizophrenia, and fewer studies have been conducted in people with FEP. In a previous study analysing 90 CSF biomarkers in people with schizophrenia at high clinical risk for psychosis (ARMS) and healthy controls, 15 analytes were differentially expressed among these groups, with a greater extent of change in the ARMS group for some analytes (Hayes et al., 2014). This study underscores the need to conduct research on CSF biomarkers in the early stages of psychosis, which could provide important clues to the mechanisms underlying psychotic disorders, allowing us to minimize confounders such as antipsychotic exposure and the neurodegenerative progression of the illness.

In the current study, we aimed to examine CSF inflammatory biomarkers in routine assays (cells, total protein, lactate dehydrogenase, glucose) that were available from a relatively large sample of FEP patients who participated in a previous study (Guasp et al., 2021). We aimed to test the potential association between CSF alterations and the clinical expression of the prodrome and the outbreak of psychosis in patients with an FEP episode. We hypothesized that negative symptoms at the FEP onset would be associated with CSF abnormalities (e.g., increased protein concentrations). As a secondary aim, we explored whether CSF alterations are associated with specific psychopathological symptoms or with the confirmation of a clinical diagnosis (schizophrenia/schizoaffective disorder vs bipolar disorder/unipolar psychotic depression) one year after the onset of psychosis.

2. Methods

2.1. Study design and participants

Patients experiencing FEP admitted to acute inpatient units (adult or child and adolescent units) from the Department of Mental Health at the Hospital of Mataró between 1 June 2018 and 31 March 2020 were offered to participate in the study. FEP was defined as new-onset disorganized behavior accompanied by delusions or hallucinations not caused by drugs that met DSM-IV criteria for a psychotic disorder (schizophrenia, bipolar disorder or unipolar major depression with psychotic features, schizophreniform disorder, brief psychotic disorder, delusional disorder, psychotic not otherwise specified). Patients were excluded if they had (1) positive symptoms of psychosis lasting more than 6 months; (2) treatment with antipsychotics for more than 6 weeks; (3) a past history of positive symptoms of psychosis; (4) a previous diagnosis of intellectual disability (IQ < 70), or (5) active medical or neurological diseases that could explain the current symptoms. The final sample, which comprised 95 FEP patients, partially overlaps with the sample of a previous study (Guasp et al., 2021) that explored different hypotheses.

The study received approval from the local Ethics Committees (Hospital of Mataró, Barcelona, Spain). All participants were informed about the nature of the study and gave written informed consent for participating in the study.

2.2. Clinical assessment

During the first week of hospital admission, all patients underwent psychiatric and neurological evaluations. The description of the clinical and biological assessment is described in Fig. 1. Two trained attending psychiatrists carried out diagnostic interviews using the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1994) for $\geq$18 years, the Schedule for Affective Disorders and Schizophrenia for school-age children and the Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) for <18 years.

The onset of prodromal and psychotic symptoms was assessed retrospectively by means of a semistructured interview with a specific ad hoc inventory (Supplementary Material: Quick Psychosis Onset and Prodromal Symptoms Inventory [Q-POPSI]) that was designed for being administered to patients and family and/or close relatives. In brief, this inventory inquired about the dates of the onset of the first prodromal symptoms or psychotic symptoms and the date of the start of the first antipsychotic treatment. The DUI and DUP were calculated. DUI was defined as the difference in time between the onset of the first symptom (prodromal or psychotic) of the illness and the start of the antipsychotic treatment. DUP was defined as the difference in time between the onset of the first positive psychotic symptom and the start of antipsychotic treatment. Six types of prodromal symptoms (symptoms occurring before the appearance of the first psychotic symptom [delusions, hallucinations or disorganization]) were assessed: 1) cognitive symptoms, 2) negative symptoms, 3) attenuated positive symptoms, 4) mood symptoms, 5) anxiety symptoms, and 6) obsessive-compulsive symptoms. The presence and duration (<1 month; 1–6 months; >6 months) of

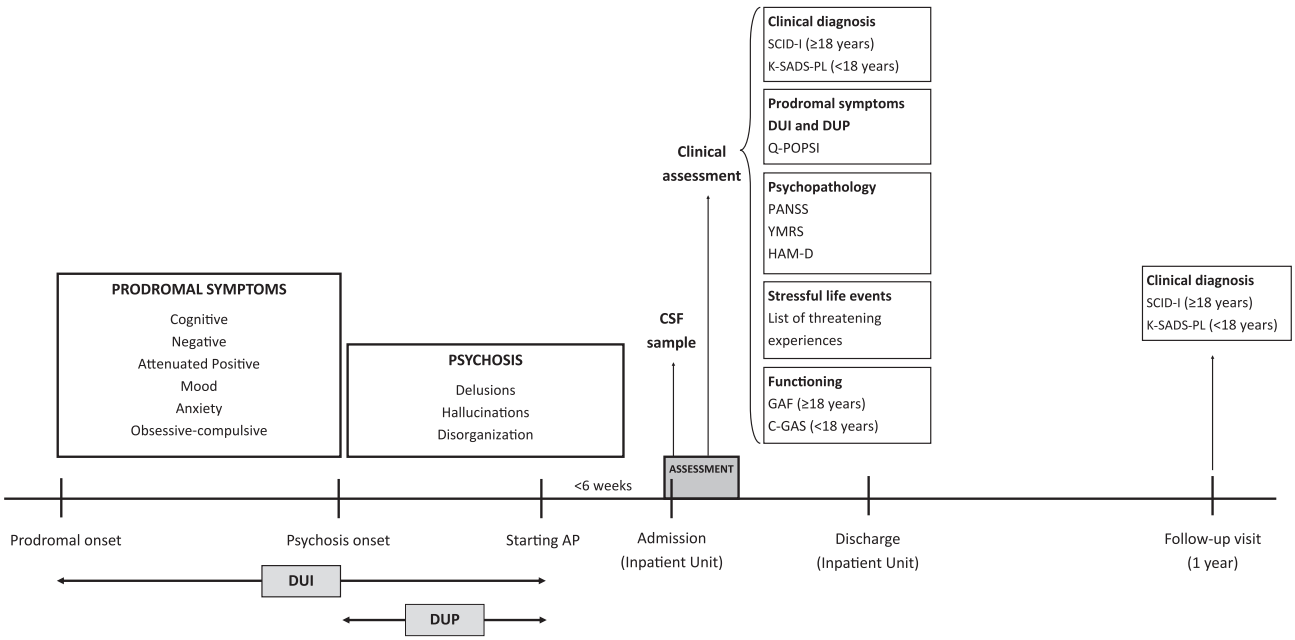

Fig. 1. Scheme of the longitudinal clinical assessments.

each type of prodromal symptom was registered. A full explanation of the Q-POPSI inventory is described in the Supplementary Material.

Psychopathology at admission was assessed using three psychometric scales. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess positive, negative and general psychopathology symptoms. Symptoms were recoded into five subscales considering the Wallwork et al. (2012) consensus: positive, negative, disorganized/concrete, excited and depressed factors. The Young Mania Rating Scale (YMRS; Lukasiewicz et al., 2013; Young et al., 1978) was administered to assess manic symptoms. The Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960; Zimmerman et al., 2013) was also administered to assess depressive symptoms.

Stressful life events that occurred during the 6 months prior to admission were assessed using The List of Threatening Experiences (Brugha and Cragg, 1990), a subset of 12 life event categories that are associated with considerable long-term contextual threat.

Functional outcome was assessed at admission and discharge from the Acute Inpatient Unit using the Global Assessment of Functioning Scale (GAF) (Hall, 1995) for ≥18 years and the Children's Global Assessment Scale (C-GAS) (Shaffer, 1983) for <18 years.

2.3. Routine CSF studies

A lumbar puncture was performed in all participants by a neurologist, either at the emergency department before admission or at the inpatient unit during the first week of admission. All participants were studied for NMDAR-Abs and GAD65-Abs in their CSF while they participated in another study dealing with autoimmune encephalitis in psychosis (Guasp et al., 2021). None of them had a diagnosis of encephalitis.

CSF was examined for blood cell counts (ref <5/μL) performed on a Sysmex XN 1000 (Sysmex Corporation, Japan) automatic counting versus manual counting chamber. Quantitative determination of glucose, total protein and lactate dehydrogenase was performed on a COBAS INTEGRA (Roche Diagnostics, Spain) using the hexokinase method (glucose), the Biuret method (total protein) and the lactate to pyruvate reaction in N-methylglucamine buffer (lactate dehydrogenase [LDH]), respectively. The sensitivity of the assays was 4.35 mg/dL for glucose, 4 mg/dL for total proteins, and 10 (IU/L) for LDH. The intra-assay and inter-assay coefficients of variation for glucose were 0.8% and 2.5% for glucose, 2.25% and 5% for total proteins, and 1.29% and 1.7% for LDH.

2.4. Statistical analysis

All data analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corporation, USA). Continuous CSF parameters (glucose, total proteins, LDH) were log transformed (ln) to reduce skewness and normalize them before conducting parametric analyses and regression analyses.

Spearman and Pearson correlation tests were used to explore associations between variables. Partial correlation analyses were used to adjust for covariates. For comparing continuous data between groups (e.g., psychiatric diagnoses at 12 months), ANOVA was used. Post hoc ANOVA analyses were adjusted for multiple comparisons using a Bonferroni adjustment. Statistical significance was set as a p value < 0.05 (two-tailed).

Regarding the cell count in the CSF, as only 3 patients had pleocytosis (>5 white blood cells/μL in CSF), we decided not to explore associations between this CSF measure and symptoms or diagnoses in the multivariate analyses. Therefore, all hypotheses on CSF variables considered three parameters that were treated as continuous variables (total protein, LDH and glucose).

Multiple linear regression analyses were used to test the first hypotheses exploring the association between prodromal symptoms and/or psychopathology symptoms at assessment and CSF biochemical parameters. In these analyses, we developed three independent equations (one for each CSF parameter [glucose, total protein, LDH], which was considered the dependent variable). A two-step hierarchical multiple linear regression was conducted. In the first step, the following independent variables were included: age, female sex, cannabis use, and number of stressful life events. As smoking and cannabis use were two variables that were highly correlated, we decided to adjust the analyses only for cannabis use. In a second step, prodromal symptoms and psychopathology variables at baseline assessment were included in the equation. Prodromal symptoms were included as an ordinal variable with three categories (0: no prodromal symptoms; 1: prodromal symptoms <6 months; 2: prodromal symptoms ≥6 months). We considered a patient to have prodromal symptoms if he/she reported prodromal symptoms of at least one of the six type of prodromal symptoms. Five

psychopathology variables were also included in this second step: positive symptoms (PANSS Wallwork factor), negative symptoms (PANSS Wallwork factor), disorganized/concrete symptoms (PANSS Wallwork factor), manic symptoms (YMRS) and depressive symptoms (HAM-D). We did not include PANSS excited or depressive factors for avoiding collinearity problems with YMRS or HAM-D scores. Multicollinearity was tested with the Variation Inflation Factor (VIF). All variables had a VIF < 5 in the tested equations.

We also conducted exploratory analyses to explore partial correlation analyses (adjusted for age, sex and cannabis use) for each of the PANSS items that are included in the five Wallwork factors. The Benjamini–Hochberg method was used to control the false discovery rate (FDR) of multiple comparisons in these partial correlation analyses dealing with PANSS items.

Multinomial regression analyses were used to test the hypotheses exploring the association between CSF parameters and longitudinal diagnostic stability. In these analyses, the clinical diagnoses at follow-up (12 months) were considered the dependent variable, considering 3 categories: 1) schizophrenia or schizoaffective disorder; 2) bipolar disorder or psychotic depression; and 3) other psychotic diagnoses. The category "other psychotic diagnoses" was set as the reference category. In these analyses, CSF parameters were included as independent variables, along with other covariates (age, sex, cannabis use and stressful life events).

3. Results

Demographic, clinical and biochemical data of the sample at the baseline assessment are described in Table 1. Only a small proportion (<10%) had abnormal CSF findings.

Of all 95 patients, 43 (45.3%) did not report prodromal symptoms, 20 (21.1%) reported prodromal symptoms from one of the six assessed dimensions, 12 (12.6%) reported prodromal symptoms from two dimensions, 10 (10.5%) reported prodromal symptoms from three dimensions, 9 (9.5%) reported symptoms from four dimensions and one patient reported symptoms from all six dimensions.

The clinical diagnoses at follow-up (1 year after the onset of FEP) are described in Table 1 in the supplementary material (Table S1). We also explored whether these diagnostic groups differed in baseline clinical characteristics or psychopathology (Table S2). The group of patients with schizophrenia or schizoaffective disorder was younger than the other two groups. Cannabis use was greater in those patients with either schizophrenia/schizoaffective or bipolar disorder/unipolar depression diagnoses than in those with other psychoses. Patients with a diagnosis of schizophrenia or schizoaffective disorder also reported a longer DUI and more cognitive and negative prodromal symptoms before psychosis onset. Regarding psychopathology, patients with unipolar depression or bipolar disorder had fewer negative symptoms and more excited and manic symptoms. Patients with other psychoses reported more depressive symptoms than the bipolar disorder/unipolar depression group.

3.1. Relationship between prodromal symptoms and/or psychopathology symptoms at assessment and CSF parameters

The results of the three independent multiple linear regression analyses exploring the associations between prodromal symptoms and psychopathology and the CSF indices are described in Table 2. In the multiple linear regression analysis for CSF glucose, age, disorganized/concrete symptoms and depressive symptoms assessed with the HAM-D were significantly associated with increased glucose concentrations in CSF whereas life stress was associated with lower CSF glucose. The relationship between depressive symptoms and glucose in the CSF is also described with a scatterplot graph in the supplementary material (Fig. S1). In the multiple linear regression analysis for total proteins, female sex was associated with lower total protein concentrations in the CSF and age with higher protein concentrations. No significant associations with prodromal symptoms or psychopathology scales at initial assessment were found. In the multiple linear analysis for LDH, prodromal symptoms were associated with lower LDH concentrations in the CSF.

In the partial correlation exploratory analyses (Table S3) analysing the relationship between PANSS items included in the Wallwork factors and CSF parameters that were adjusted for age, sex and cannabis use, we did not find any significant associations between CSF total proteins and PANSS items. CSF glucose concentration was associated with difficulty in abstraction ($r = 0.225$, $p = 0.031$) and anxiety ($r = 0.269$, $p = 0.010$), although these two results did not survive the FDR adjustment with a Benjamini-Hochberg procedure. CSF LDH concentration was

Table 1
Demographic, clinical and biochemical variables of 95 patients with first episode psychosis.

Age, mean (SD), years	35.0 (15.5)
Female sex, N (%)	39 (41.1%)
Previous history of psychiatric (non-psychotic) disorders, N (%)	60 (63.1%)
Mood disorder	37 (29.5%)
Anxiety disorder	6 (6.3%)
Obsessive compulsive disorder	2 (2.1%)
Personality disorder	23 (24.2%)
Eating behavior disorder	4 (4.2)
Substance use disorder	27 (28.4)
Others	7 (7.4)
Smoking, N (%)	50 (52.6%)
Cannabis use (abuse or dependence), N (%)	47 (49.5%)
Alcohol use (abuse or dependence), N (%)	29 (30.5%)
First degree family history of psychiatric disease, N (%)	42 (44.2%)
Previous life stressful events, N (%)	41 (43.2%)
Prodromal symptoms, N (%)	52 (54.7)
Cognitive symptoms	21 (22.1%)
Negative symptoms	21 (22.1%)
Attenuated positive psychotic symptoms	27 (28.4%)
Mood symptoms	20 (21.1%)
Anxiety symptoms	23 (24.2%)
Obsessive-compulsive symptoms	4 (4.2%)
Duration of psychiatric prodromal symptoms, N (%)	
No prodromal symptoms	43 (45.3%)
<1 month	4 (4.2%)
1–6 months	23 (24.2%)
>6 months	25 (26.3%)
Duration of untreated illness, mean (SD), days	172.0 (260.2)
Duration of untreated psychosis, mean (SD), days	37.9 (51.7)
Treatment during hospital admission, N (%)	
Atypical antipsychotics	95 (100%)
Typical antipsychotics	8 (8.4%)
Mood stabilizers	47 (49.5%)
Electroconvulsive therapy	1 (1.1%)
PANSS, mean (SD)	
Total score	82.6 (20.1)
Wallwork factors:	
Positive factor	14.4 (3.5)
Negative factor	12.1 (7.0)
Disorganized/concrete factor	8.8 (2.9)
Excited factor	11.6 (4.1)
Depressed factor	8.3 (3.6)
YMRS, mean (SD)	26.8 (11.3)
HAM-D, mean (SD)	22.7 (9.8)
GAF, mean (SD)	
On admission	30.0 (6.7)
At discharge	62.6 (9.6)
Cerebrospinal fluid variables	
Parameters, mean (SD)	
Cells (cells/μL)	1.7 (1.7)
Glucose (mg/dL)	65.4 (6.3)
Total protein (mg/dL)	31.4 (11.4)
LDH (IU/L at 37°C)	27.8 (15.2)
Abnormal cerebrospinal fluid studies, N (%)	9 (9.4%)
Pleocytosis (>5 white blood cells/μL in CSF)	3 (3.1%)
Increased protein concentration (>45 mg/dL)	6 (6.3%)

Abbreviations: SD, standard deviation; PANSS, Positive and Negative Syndrome Scale, YMRS, Young Mania Rating Scale, HAM-D, Hamilton Depressive Rating Scale for Depression; GAF, Global Assessment of Functioning.

Table 2
Results of the multiple linear regression exploring the association between CSF biochemical parameters, prodromal symptoms and psychopathology at FEP onset.

		CSF glucose		CSF total proteins		CSF LDH	
		β	*p*	β	*p*	β	*p*
First model	Age	**0.220**	**0.035**	**0.346**	**0.001**	0.089	0.422
	Female sex	−0.006	0.950	**−0.236**	**0.017**	−0.019	0.857
	Cannabis use	−0.204	0.052	0.160	0.124	−0.170	0.129
	Number of stressful life events	**−0.248**	**0.012**	0.045	0.642	0.006	0.955
Last model	Age	**0.319**	**0.007**	**0.286**	**0.020**	−0.023	0.854
	Female sex	−0.061	0.547	**−0.268**	**0.014**	0.119	0.286
	Cannabis use	−0.171	0.110	0.159	0.155	−0.139	0.233
	Number of stressful life events	**−0.368**	**0.001**	0.020	0.855	−0.039	0.734
	Prodromal symptoms[a]	0.155	0.162	0.028	0.807	**−0.248**	**0.042**
	Positive symptoms (PANSS Wallwork factor)	−0.048	0.690	0.021	0.867	0.055	0.681
	Negative symptoms (PANSS Wallwork factor)	−0.274	0.149	0.118	0.551	−0.300	0.150
	Disorganized/concrete symptoms (PANSS Wallwork factor)	**0.329**	**0.023**	−0.096	0.522	0.096	0.540
	Manic symptoms (YMRS)	−0.111	0.479	0.059	0.720	−0.062	0.717
	Depressive symptoms (HAM-D)	**0.269**	**0.041**	0.226	0.100	0.221	0.123

Abbreviations: FEP, first-episode psychosis; β, standardized beta regression coefficient; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale; HAM-D, Hamilton Depressive Rating Scale. Statistically significant ($p < 0.05$) results are highlighted in bold.

[a] Prodromal symptoms were defined as an ordinal variable (0: No prodromal symptoms; 1: Prodromal symptoms <6 months; 2: Prodromal symptoms ≥ 6 months).

significantly associated with reduced social withdrawal ($r = -0.342$, $p = 0.001$) and poor impulse control ($r = 0.219$, $p = 0.036$). After controlling for the FDR, only the correlation between social withdrawal and CSF LDH concentrations survived the multiple comparisons correction. For a descriptive representation using a dichotomous variable for social withdrawal considering the cut-off point of 3, the distribution of LDH CSF concentrations is represented in Fig. S2. Of all 95 FEP patients, 41 (43.2%) reported social withdrawal.

3.2. CSF parameters and psychiatric diagnoses at the 12-month follow-up

Patients with a diagnosis of schizophrenia or schizoaffective disorder at 12 months had lower glucose baseline concentrations in the CSF than the other psychotic groups (Table S4). Post hoc ANOVA comparisons with a Bonferroni adjustment revealed that the difference was significant from other psychoses. Schizophrenia or schizoaffective disorder patients also had lower total protein concentrations than patients with bipolar disorder or major depression with psychotic features (Table S4). There were no significant differences in LDH concentrations between diagnoses.

In the multinomial logistic regression analyses adjusted for age, sex, cannabis and stressful life events, and considering all three CSF parameters as independent variables, glucose concentrations in the CSF were associated with a lower risk of having schizophrenia or schizoaffective disorder at follow-up (which suggests that lower baseline glucose concentrations at baseline were found in the schizophrenia or schizoaffective disorder group). The results of this analysis are described in Table 3.

4. Discussion

In our study that included 95 FEP patients, CSF biomarkers that can be assessed in routine clinical practice were associated with the clinical phenotype in terms of prodromal symptoms (lower LDH associated with prodromal symptoms) or psychopathology at the onset of the illness (higher CSF glucose associated with depressive symptoms and disorganized/concrete symptoms; lower LDH with social withdrawal). Moreover, CSF glucose was a predictor of the long-term diagnosis (lower CSF concentrations were associated with schizophrenia or schizoaffective disorder diagnoses). However, it is important to underscore that most patients had CSF biomarkers within the normal range, and < 10% of participants had abnormal CSF indices.

On the one hand, prodromal symptoms were associated with lower LDH concentrations in the CSF, and we found a significant negative association between social withdrawal and CSF LDH concentrations. No previous studies have explored the clinical correlates of CSF LDH levels

Table 3
CSF paremeters at baseline visit and psychiatric diagnoses at follow-up (12 months).

Diagnosis at 12 months		B	SE	p	OR	CI 95% OR	
						Lower limit	Upper limit
Schizophrenia or Schizoaffective disorder	Intercept	**18.66**	**6.83**	**0.006**			
	CSF LDH	−0.77	0.70	0.271	0.47	0.12	1.81
	CSF Total Proteins	−1.65	1.24	0.185	0.19	0.02	2.20
	CSF glucose	**−0.13**	**0.07**	**0.043**	**0.88**	**0.77**	**0.99**
	Age (years)	**−0.07**	**0.04**	**0.049**	**0.93**	**0.87**	**1.00**
	Cannabis use	0.57	0.80	0.476	1.77	0.37	8.54
	Number of stressful life events	0.28	0.35	0.424	1.32	0.67	2.62
	Female sex	−1.06	0.78	0.176	0.35	0.08	1.61
Bipolar disorder or unipolar psychotic depression	Intercept	4.04	4.73	0.393			
	CSF LDH	−0.21	0.53	0.691	0.81	0.29	2.30
	CSF Total Proteins	0.38	0.93	0.680	1.47	0.24	9.11
	CSF glucose	−0.06	0.05	0.183	0.94	0.85	1.03
	Age (years)	0.01	0.02	0.638	1.01	0.97	1.05
	Cannabis use	1.07	0.66	0.103	2.92	0.81	10.63
	Number of stressful life events	0.06	0.30	0.847	1.06	0.59	1.89
	Female sex	−0.55	0.60	0.353	0.57	0.18	1.85

This multinomial logistic regression analysis considered "other psychoses" as the reference category.
Abbreviations: CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; SE, standard error, CI, Confidence interval; OR, Odds ratio.

in FEP patients. LDH is an enzyme of the glycolysis energy pathway that reduces pyruvate into lactate and represents the intersection of key pathways of energy metabolism. Decreased expression levels of LDH indicate abnormal or possibly decreased brain energy production. These results fit well with a proteomics research review of schizophrenia (Davalieva et al., 2016), which included three postmortem human studies where dysregulation of the LDH complex (LDHA/B) in the anterior cingulate cortex (ACC), cortex callosum (CC) and hippocampus was observed. These findings suggest that lower LDH levels in the CSF could be a biomarker in FEP for prodromal and negative symptomatology (especially social withdrawal), both relevant indicators of a poor long-term outcome. LDH can also regulate transcription by regulating the cellular redox state (Valvona et al., 2016). It participates in metabolic and inflammatory processes that could be involved in brain development and functioning. Lactate is also considered an intracellular neuronal messenger, which is used as a fuel and modulates the activity of multiple molecular targets, affecting functions at the cellular and organ level (Barros, 2013). However, further research is required to determine its precise role.

Previous studies have identified alterations of metabolic biomarkers in schizophrenia patients that are indicative of perturbations in glucoregulatory pathways (Guest et al., 2011, 2010; Herberth et al., 2011; Holmes et al., 2006; Schwarz et al., 2012). We found that patients with a diagnosis of schizophrenia or schizoaffective disorder at 12 months had lower glucose baseline concentrations in the CSF than the other psychotic groups. Additionally, increased glucose concentrations in the CSF were associated with disorganized/concrete symptoms and depressive symptoms at the onset of the illness assessed with the HAM-D. Glucose utilization and therefore energy production are known to coexist with synaptic activity and plasticity. Growing evidence, from molecular to neuroimaging, has implicated impaired brain energy metabolism, characterized by brain glucose utilization abnormalities, mitochondrial dysfunction, and high-energy phosphate molecule depletion in psychosis pathophysiology (Clay et al., 2011). Accumulated evidence highlights that bioenergetic systems and synaptic functions (especially the glutamatergic system) are abnormal in psychiatric illnesses such as schizophrenia (Sullivan et al., 2018). In previous studies from our group, glycated haemoglobin was associated with poor cognitive function in people with recent-onset psychosis (Montalvo et al., 2020). Other groups have also reported an association between glucose intolerance and more severe negative symptoms in first-episode drug-naïve patients with schizophrenia (Chen et al., 2016). Our results of a positive association between disorganized/concrete symptoms and increased CSF glucose parameters are in accordance with these previous studies and suggest that a more severe phenotype in first-episode psychosis is associated with glucose abnormalities. It is important to underscore that the disorganized/concrete Wallwork factor accounts for the largest share of the PANSS association with cognition (Wallwork et al., 2012). Another study (Tomasik et al., 2019) conducted in first episode, antipsychotic-naïve patients with schizophrenia demonstrated an association between a schizophrenia polygenic risk score and insulin resistance, suggesting that insulin resistance is a hallmark of schizophrenia. Moreover, insulin resistance was also associated with diminished antipsychotic response to antipsychotic treatment (Tomasik et al., 2019). However, it is important to underscore that no other studies have explored the clinical correlates of glucose concentrations in the CSF of patients with first-episode psychosis, and our findings need to be replicated in other cohorts.

In summary, the correlations we found between clinical features and diagnoses at 12 months with routine CSF parameters associated with the glucose pathway (LDH and glucose in CSF) highlight the importance of bioenergetic systems as possible therapeutic targets.

Patients diagnosed with schizophrenia or schizoaffective disorder at 12 months also had lower total protein concentrations than patients with bipolar disorder or major depression with psychotic features. This finding suggests that biological differences related to the permeability of the blood-brain barrier (BBB) could already be present in the early stages between these two groups (non-affective versus affective psychoses). This result would be in line with that found in a recent study (Endres et al., 2020), where CSF protein levels were more frequently increased in patients with affective disorders compared to schizophreniform syndromes.

Our study had several limitations that need to be acknowledged. First, the original project was initially designed to study autoimmunity in the CSF and serum, and our study is a secondary analysis, as we had available information on routine CSF biomarkers that was not explored in our previous study (Guasp et al., 2021). However, the original project was not designed to control for factors that could affect the bioenergetic system (such as assessing dietary habits or performing lumbar puncture under fasting conditions). We did adjust multivariate analyses for life stress, which may affect the disruption of glucose energy metabolites in the CSF (Qin et al., 2019). Second, prodromal symptoms were retrospectively assessed with a semistructured interview, and recall bias may exist. The Q-POPSI inventory was designed as an ad hoc inventory for our study and conceived as a brief instrument for assessing information relative to the psychosis onset and prodromal phase. Although it has not been cross-validated with other instruments (e.g., IRAOS [(Häfner et al., 1992)] or ER-IRAOs [(Maurer et al., 2004)]) that take longer to administrate (30–60 min), we are currently working on its validation in an independent sample of FEP patients. Third, the FEP patients were receiving antipsychotic treatment and were not drug-naïve. However, we aimed to reduce any long-term treatment effects by excluding those patients who had received antipsychotic treatment for a period longer than 6 weeks. Finally, we only considered CSF analytes that might be determined in routine clinical practice. Further research might incorporate extended analyses (e.g., proteomics and metabolomics) to improve early diagnosis, disease stratification, therapeutic choice and outcome prediction in FEP patients. These approaches, along with artificial intelligence, would allow for testing large numbers of proteins for associations with these diseases and may contribute to the understanding of the molecular mechanisms of psychotic disorders.

In summary, our study suggests that CSF biomarkers related to bioenergetic systems are associated with prodromal symptoms and the phenotype of psychotic disorders during the early stages of the disease.

Authors' contributions

EGS: Conceptualization; Investigation; Methodology; Resources; Data curation; Formal analysis; Project administration; Writing - original draft; Writing-review & editing. MMR: Investigation; Resources; Writing - review & editing; EBQ: Investigation; Resources; Writing - review & editing; EVD: Investigation; Resources; Writing - review & lEditing. NG: Investigation; Resources; Writing - review & editing; VC: Investigation; Resources; Writing - review & editing. DM: Investigation; Resources; Writing - review & editing; CTR: Investigation; Resources; Writing - review & editing. BCF: Methodology; Writing - review & editing. JL: Conceptualization; Methodology; Funding acquisition; Formal analysis; Software; Visualization; Supervision; Writing - review & editing.

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Declaration of Competing Interest

The authors declare no conflict of interest regarding this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110424.

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