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ORIGINAL CONTRIBUTION

Differences in the regulation of inflammatory pathways in adolescent- and adult-onset first-episode psychosis

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Abstract

A precise description of the inflammatory response in first-episode psychosis (FEP) by age of onset does not exist. We explored baseline and 6-month follow-up differences in the pro/anti-inflammatory balance in plasma and peripheral blood mononuclear cells in adolescent-onset FEP (≤ 18 y.o., $N=27$) and adult-onset FEP (≥ 25 y.o., $N=43$) using non-parametric 1-category ANCOVA, with age group as an independent variable and values of pro- and anti-inflammatory markers at baseline and at follow-up as dependent variables. We used a non-parametric repeated-measures mixed-effects model to explore the baseline/6-month change in pro- and anti-inflammatory markers within adolescent- and adult-onset groups, exploring differential trajectories of change by means of the interaction of time by age-of-onset group. Levels of the nuclear transcription factor (NFκB), a master regulator of the inflammatory and oxido/nitrosative status of cells, were higher in adolescent-onset FEP both at baseline and after 6 months. During follow-up, we found further increases in levels of soluble inflammatory markers (PGE_2 and NO_2^-) only in adolescent-onset FEP. In contrast, in adult-onset FEP, the expression of inducible NO synthase (iNOS), which is also pro-inflammatory, tended to decrease, with no further increase in other pro-inflammatory markers. Significant differences in the direction of change by age-of-onset cohort exist only for NFκB ($F=4.165$, $df=2$, 70.95, $p=0.019$). Our results support the existence of changes in the pro/anti-inflammatory balance in FEP depending on the neurodevelopmental stage at illness onset. These results also suggest that inflammation may be a potential therapeutic target in adolescent-onset FEP.

Keywords Inflammation · Psychosis · Early-onset psychosis · Inflammatory pathways

Introduction

Psychotic disorders are a major cause of disability and functional impairment worldwide [1]. Although most psychotic disorders appear or show their first symptoms before adulthood [2], there is still much to learn regarding aetiopathogenic particularities of psychotic disorders depending on the developmental stage at onset.

Previous research has identified clinical differences between patients with psychosis depending on age of onset. Early-onset psychotic cases, defined as those in which positive psychotic symptoms start prior to age 18, have been shown to have longer time to symptom remission [3] as well as greater cognitive impairment [4] and more severe psychopathology [4-6] compared to those that start during adulthood. These and other studies have associated early-onset psychotic cases with poorer prognosis [7], although others have not [8, 9].

Reports are emerging of underlying biological differences in psychotic patients depending on age of onset. For example, parental psychosis was more frequent in patients with childhood-onset schizophrenia than in those with illness onset in adulthood [10]. Dysbindin-1, a gene linked to schizophrenia

FLAMM-PEPs is a multicentre, collaborative and translational research group within CIBERSAM whose aim is to study inflammatory pathways in psychosis, both as possible biomarkers and as possible new therapeutic targets. FLAMM-PEPs is now part of the PEPs study, a Spanish project for research into first-episode psychosis.

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risk, has a different haplotypic risk pattern in families with early-onset psychosis cases than it does in those with late-onset psychosis cases [11]. Structural brain abnormalities in patients with first episodes of affective and schizophrenia spectrum psychosis and age of onset of psychosis follow a non-linear relationship [12]. Interestingly, these findings were less evident when using linear statistical approaches to assess the effect of age, which suggests that researchers may need to account for the heterogeneity of typical brain maturation when designing biological approaches to the study of psychosis [12].

Inflammation may be a mediator in psychotic symptomatology associated with poorer clinical outcomes in first-episode psychosis (FEP) [13]. In a previous study, we found that imbalances in inflammation-controlling mechanisms play a role in the early stages of psychosis, before confounding factors such as the use of psychotropic treatments or illicit drugs, disease progression and comorbid conditions can act [14]. Exposure to inflammation during critical periods of brain development can affect cell differentiation, survival, and function [15] and contribute to sensitization of dopamine neurons [16], and changes in serotonin metabolism [17]. Such changes may predispose patients to earlier onset of neurodevelopmental illnesses such as psychosis.

We previously found that, compared with healthy controls, patients with FEP had active inflammatory processes at both the plasma and the cellular level, along with a significant decrease in the anti-inflammatory response at the beginning of the psychotic symptoms phase [14] The effect persisted one year after the onset of psychosis [18]. However, findings in younger subjects are disputed. A recent meta-analysis reporting on inflammatory and oxidative stress aspects linked to early-onset FEP found only a few heterogeneous parameters that differed significantly between patients and controls, preventing the authors from defining a homogeneous pattern [19].

To our knowledge, no study has reported on the role of inflammatory processes and specific components of the pro- and anti-inflammatory cascade in psychosis at different developmental stages. This exploratory study intends to address the inflammation and oxidative stress profile in psychotic disorders depending on age of onset, a proxy for the developmental stage. Its aim is to explore whether there are differences in the pro/anti-inflammatory balance in plasma and peripheral blood mononuclear cells (PBMC) in patients with adolescent-onset FEP and patients with adult-onset FEP and, if found, to explore whether these differences last through the follow-up period.

Methods

Subjects

This study draws data from FLAMM-PEPs, a naturalistic 6-month longitudinal study of patients with first-episode psychosis (FEP) and matched controls consecutively recruited from in- and outpatient units in Spain [14]. Subjects included in this analysis met the following inclusion criteria: age between 9 and 35 years, duration of psychotic symptoms within a psychotic episode of ≤ 18 months, and speak fluent Spanish. Controls were recruited in the same geographical areas as patients and were matched with patients by gender, age (± 10%), and parental socioeconomic status (± 1 level difference in the Hollingshead-Redlich scale [20]). Controls could not have lifetime DSM-IV psychiatric disorders or a history of psychotic disorders among first-degree relatives and had to speak fluent Spanish. The exclusion criteria for patients and controls were mental retardation (DSM-IV criteria: IQ < 70, together with impaired functioning), history of traumatic head injury with loss of consciousness, and history of organic disease with mental repercussions. Neither the FEP patients nor the healthy control subjects were receiving immunosuppressive drugs or vaccinations for at least 6 months prior to inclusion in the study or anti-inflammatory analgesics the 2 days prior to the extraction of the blood sample.

This research complies with the latest version of the Declaration of Helsinki. We obtained written informed consent from all participants after a complete description of the study and the nature of the procedures. In the case of minors, parents/legal guardians gave their written consent and the minors agreed to participate. The Ethics Committees of all the participating centres approved the study. We wished to account for neurodevelopmental stage, especially in brain regions associated with psychosis [21, 22], and to maximize potential differences in variables of interest due to age of onset of psychosis, taking into consideration the heterogeneity of typical brain maturity and the non-linear effect of age on brain development in previous studies [12]. So we chose to select 2 groups of patients to be included in these analyses, namely, those with onset of psychosis ≤ 18 years (adolescent-onset), and those with onset ≥ 25 years (adult-onset, following previous literature [6]), despite the limitations this might put on the generalisability of the findings.

Clinical assessments

Our clinical assessments followed those described in Bernardo et al. [23]. Experienced psychiatrists evaluated the participants. Semi-structured diagnostic interviews were used to establish DSM-IV diagnoses, the Structured Clinical Interview for DSM Disorders (SCID) in adults [24], and the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) in minors [25]. We assessed psychopathology using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) [26], the Young Mania Rating Scale (YMRS) [27], and the Montgomery-Asberg Depression Rating Scale (MADRS)

[28]. Functioning was assessed using the Children's Global Assessment Scale [29] or the Global Assessment of Functioning scale [30], depending on age. We express antipsychotic drug doses as chlorpromazine equivalents [31]. Onset of psychotic symptoms was determined using the Symptom Onset in Schizophrenia (SOS) inventory [32]. We also recorded the duration of untreated psychosis (number of days elapsed between onset of psychosis and initiation of antipsychotic treatment) and the number of days between onset of FEP and blood sampling. Clinical assessments included a complete medical history and physical examination, laboratory tests, and body mass index (BMI in kg/m^2).

Biochemical determinations

Specimen collection and preparation

Participants supplied venous blood samples (10 mL) between 8:00 and 10:00 h after fasting overnight. Blood tubes were centrifuged ($641g \times 10$ min, 4 °C) and the resultant plasma samples stored at –80ºC. The rest of the sample was diluted in culture medium (RPMI 1640, InvitrogenR), and a gradient with Ficoll-PaqueR (GE HealthcareR) was used to isolate mononuclear cells by centrifugation ($800g \times$ 40 min, RT). The PBMC layer was aspirated, resuspended in RPMI, and centrifuged ($1116g \times 10$ min, RT). The supernatant was removed and the mononuclear cell-enriched pellet was stored at –80 °C.

Biochemical determinations in plasma

Prostaglandins, including COX by-products, PGE_2 and 15d-PGJ_2, were determined by enzyme immunoassay (EIA) using Cayman Chemicals and DRGR Diagnostics, respectively. Nitrites (NO_2), the final and stable product of NO, were determined by Griess method. Lipid peroxidation was assessed using the thiobarbituric acid reactive substances (TBARS) assay (Cayman). Cotinine levels, the major degradation product of nicotine metabolism, were determined by EIA (Cozart).

Biochemical determinations in peripheral blood mononuclear cells (PBMC)

PBMC samples were first fractionated into cytosolic and nuclear extracts. In the nuclear extracts, the pro-inflammatory p65 NFB subunit and anti-inflammatory PPAR transcriptional activities were determined.

To determine the nuclear factor kappa B (NFκB) activity, the presence of the p65 subunit in cell nuclei, considered an index of activity, was measured using a transcription factor assay from Cayman Chemicals. PPAR transcription factor activity was determined using ELISA-based kits also from Cayman Chemicals. Protein levels of NFκB inhibitory subunit IB, COX2, and iNOS were quantified using Western blot in cytosolic extracts from PBMC. The housekeeping gene β-actin was used as a loading control. See Garcia-Bueno et al. [14, 18] for methodological details.

Statistical analysis

First, we compared adolescent-onset FEP and adult-onset FEP in terms of sociodemographic and clinical characteristics. We analysed categorical data using the Chi-square test. In the case of continuous variables, after verifying normality using the Kolmogorov–Smirnov test, we used *t* test or Mann–Whitney tests as appropriate.

Regarding analyses of pro- and anti-inflammatory parameters, we used Kolmogorov–Smirnov and Shapiro–Wilk tests to test for normality and found non-normal distributions of most of the parameters both at baseline and at follow-up. Therefore, since non-parametric tests provide more conservative results, we imputed the ranks of the data and evaluated baseline and follow-up differences in these parameters between the 2 different age-of-onset groups using non-parametric one-category ANCOVA [33], with age group as an independent variable and values of pro- and anti-inflammatory markers at baseline and at follow-up as dependent variables. A non-parametric repeated-measures mixed-effects model was used to explore the baseline/6-month change in pro- and anti-inflammatory markers within adolescent- and adult-onset groups, exploring differential trajectories of change by means of the interaction of time and age-of-onset group.

Variables that differed significantly between the groups in the bivariate analyses were included as covariates in the analyses. Additionally, we performed correlation analyses of factors associated with inflammation in the literature (BMI, antipsychotic medication, sex, cotinine, cannabis use) and found that only the level of cotinine (which is more sensitive than reported tobacco use) and sex were correlated with levels of pro- and anti-inflammatory markers in our sample. Therefore, the final covariates included in the analyses were days since the first psychotic symptoms until the baseline visit, age at onset of cannabis use, cotinine level, and sex.

We managed and analysed our data in SPSS (version 20.0). All tests were 2-tailed, and statistical significance was set at $p < 0.05$.

Results

The study population comprised 27 adolescent-onset FEP patients (mean age 16.85 ± 1.38, age-range 12–19) and 43 adult-onset patients (mean age 29.93 3.14, age-range 25–35).

All adolescent-onset patients had onset of psychotic symptoms before 18 years of age.

Sociodemographic and clinical characteristics

Age at onset of cannabis use was lower in patients with adolescent-onset psychosis compared to patients with adult-onset psychosis (14.18 ± 1.39 vs 18.61 ± 3.13, $p = 0.015$); time from first psychotic symptom to baseline visit was longer in adolescent-onset patients (264.07 ± 126.0 vs. 397.67 ± 141.42 days, $p < 0.001$). There were no significant differences by age-of-onset group in sex, race, socioeconomic status, duration of untreated psychosis, percentage of affective/non-affective psychosis, psychopathology scores, functioning, antipsychotic treatment, total dose of antipsychotics in chlorpromazine equivalents, lithium treatment, body mass index, tobacco use, cotinine level, and cannabis use (Table 1). There were no significant differences in sociodemographic or clinical characteristics between patients with only baseline data ($N = 12$) and those with baseline and follow-up assessments ($N = 58$) (data not shown).

Baseline and 6-month differences in pro/anti-inflammatory levels in FEP by age of onset

To avoid misattributing to age of onset differences that could be due to normal development, we first compared baseline pro- and anti-inflammatory data between 2 groups of healthy controls matched by age and gender with the patient samples resembling the age distributions of the FEP patients ($N = 24$, mean age 17.25 ± 2.59, age-range 12–19; $N = 58$, mean age 30.12 ± 4.22, age-range 25–35). None of the pro- and anti-inflammatory parameters studied had statistically significant differences in both age-range groups (Table 2), in line with previously published reports [34].

At baseline, only expression of the inflammatory nuclear transcription factor NFκB in PBMCs was significantly different between both patient groups. It was higher in patients with adolescent-onset FEP (Table 3). At follow-up, NFκB expression and levels of the inflammatory prostaglandin E2 (PGE_2) in plasma were also higher in the adolescent-onset group, whereas plasma levels of stable nitric oxide metabolites (NO_2) were higher in the adult-onset group. Differences between groups in the remaining parameters were not statistically significant (Table 3).

Differential within-group baseline/6-month change in pro- and anti-inflammatory markers

In adolescent-onset FEP, PGE_2 and NO_2^- (pro-inflammatory and oxidative markers) were the only parameters that increased significantly from baseline to the 6-month follow-up visit, while other parameters did not experience significant changes between these 2 time points. In adult-onset FEP, the expression of inducible NO synthase (iNOS), which is also pro-inflammatory, tended to decrease within the same period, with no further increase in other pro-inflammatory markers (Table 3). Significant differences in the direction of change by age-of-onset cohort were only found for NFκB ($F = 4.165$, df = 2, 70.95, $p = 0.019$). A sensitivity analysis including only subjects with assessments at both time points found baseline to follow-up changes only in NFκB. This analysis found a significant increase in NFkB from baseline to follow-up in both age of onset cohorts (adolescent-onset $F = 9.59$, $p = 0.005$; adult-onset $F = 7.72$, $p = 0.011$) and replicated the finding of significant differences in the direction of change of NFkB, with larger changes in the earlier-onset patients ($F = 3.484$, df = 2, 23.41, $p = 0.047$).

Discussion

To our knowledge, this is the first study to explore differences in the complex intra- and intercellular pathways controlling inflammation and oxidative stress in FEP by age of onset. We showed that levels of NFκB, a master regulator of the inflammatory and oxido/nitrosative status of cells, were higher in patients with adolescent-onset FEP, both at baseline and after 6 months of follow-up, compared to patients with adult-onset FEP. During follow-up, only patients with adolescent-onset FEP experienced a further increase in some soluble inflammatory markers (PGE_2 and NO_2^-). Interestingly, only patients with adult-onset FEP experienced a decrease in other markers (iNOS) during follow-up.

Differences in the regulation of inflammatory balance were previously analysed in the whole FEP sample (from 12 to 35 y.o.) at both baseline and 6-month follow-up timepoints [14, 18]. The main difference between adolescent-onset FEP in this study and the results reported previously for the whole sample is the increased levels of the intracellular pro-inflammatory nuclear transcription factor (NFκB) in the adolescent-onset FEP in both baseline and follow-up conditions compared to the adult-onset patients. This increase is not present in the whole sample. As a singular similarity, plasma levels of the inflammatory and oxidative prostaglandin E2 increased over time (baseline to follow up) in adolescent-onset and in the whole FEP sample, whereas iNOS levels decreased both in the whole FEP sample and the adult-onset group. The fact that the rest of the baseline to follow-up alterations found in the whole sample (increased COX-2 expression, TBARS levels, and decreased anti-inflammatory mediators 15d-PGJ2 and PPARγ) were absent in the present study in both adolescent- and adult-onset FEP groups, suggests the existence of specific changes in the adolescent-onset group in the inflammatory response

Table 1 Baseline sociodemographic and clinical characteristics in first-episode psychosis with onset at ≤ 18 and at ≥ 25 years

Demographic characteristics	Onset ≤ 18 years ($n=27$)	Onset ≥ 25 years ($n=43$)	X^2/F t/U	p
Age, mean (SD)	$N=27$ 16.85 (1.38)	$N=43$ 29.93 (3.14)		
Sex: male	$N=27$ 21 (77.8)	$N=43$ 28 (65.1)	$X^2=1.27$	0.26
Race: Caucasian	$N=27$ 25 (92.6)	$N=43$ 40 (93.0)	$X^2=5.07$	0.41
Socioeconomic status	$N=27$	$N=43$	$X^2=4.39$	0.36
High	8 (29.6)	5 (11.6)		
Medium-high	3 (11.1)	5 (11.6)		
Medium	8 (29.6)	12 (27.9)		
Medium-low	6 (22.2)	16 (37.2)		
Low	2 (7.4)	5 (11.6)		
Psychiatric history				
Duration of untreated psychosis – days*, mean (SD)	$N=20$ 97.45 (114.82)	$N=35$ 66.49 (82.82)	$U=331.0$	0.74
Days from first psychotic symptom to baseline visit, mean (SD)	$N=27$ 397.67 (141.42)	$N=43$ 264.07 (126.03)	$t=4.12$	< **0.001**
Diagnosis	$N=27$	$N=43$	$X^2=0.68$	0.41
Affective psychosis	8 (29.6)	9 (20.9)		
Non-affective psychosis	19 (70.4)	34 (79.1)		
Psychopathology scores				
Positive and Negative Syndrome Scale for Schizophrenia	$N=27$	$N=43$		
Total*	51.22 (21.38)	55.40 (21.47)	$U=514.0$	0.43
Positive*	11.30 (7.02)	11.40 (6.49)	$U=576.5$	0.96
Negative*	13.33 (4.76)	15.65 (7.25)	$U=492.5$	0.29
General*	26.69 (11.86)	28.35 (10.68)	$U=505.5$	0.37
Young mania rating scale*	$N=27$ 3.11 (5.84)	$N=43$ 1.23 (2.56)	$U=476.0$	0.14
Montgomery–Asberg depression rating scale*	$N=26$ 5.77 (5.92)	$N=39$ 6.95 (7.05)	$U=459.0$	0.52
Global assessment of functioning	$N=27$ 67.07 (14.75)	$N=43$ 65.33 (15.75)	$t=0.46$	0.65
Treatment				
Baseline antipsychotic medication	$N=27$ (100.0)	$N=43$ (100.0)	$X^2=2.01$	0.96
Risperidone	6 (22.2)	14 (32.6)		
Olanzapine	4 (14.8)	6 (14.0)		
Aripiprazole	3 (11.1)	5 (11.6)		
Paliperidone	2 (7.4)	3 (7.0)		
Clozapine	2 (7.4)	2 (4.7)		
Quetiapine	2 (7.4)	3 (7.0)		
Ziprasidone	0 (0)	1 (2.3)		
None	8 (29.6)	9 (20.9)		
Total antipsychotic dose (chlorpromazine equivalents)*	$N=27$ 240.18 (233.42)	$N=43$ 251.74 (212.95)	$U=547.00$	0.68
Lithium use	$N=27$ 2 (7.4)	$N=43$ 5 (11.6)	$X^2=0.33$	0.45
BMI and substance use				
Baseline body mass index (BMI), mean (SD)	$N=25$ 24.05 (4.03)	$N=41$ 25.33 (3.86)	t=-1.29	0.20
Baseline cannabis use	$N=27$ 6 (22.2)	$N=43$ 7 (16.3)	$X^2=0.39$	0.54

Table 1 (continued)

Demographic characteristics	Onset ≤ 18 years ($n=27$)	Onset ≥ 25 years ($n=43$)	X^2/F t/U	p
Baseline cannabis per month (a), mean (SD)*	$N=6$ 1.67 (0.92)	$N=7$ 23.14 (13.88)	$U=18$	0.64
Cannabis lifetime use	$N=27$ 11 (40.7)	$N=43$ 18 (41.9)	$X^2=0.01$	0.93
Cannabis use age of onset (b), mean (SD)	$N=11$ 14.18 (1.33)	$N=18$ 18.61 (3.13)	$t=6.79$	**0.015**
Time of cannabis use (years) (b), mean (SD)*	$N=11$ 3.45 (3.64)	$N=18$ 5.72 (4.63)	$U=73$	0.24
Cotinine level, mean (SD)	$N=19$ 83.53 (76.57)	$N=32$ 76.91 (88.01)	$t=288.5$	0.76
Baseline tobacco consumption (cigarettes/month)(c), mean (SD)	$N=10$ 391.40 (176.68)	$N=27$ 359.41 (243.39)	$U=128.50$	0.82

Data are shown as No. (%) unless otherwise indicated

*Mann–Whitney U test

(a) Including current cannabis users

(b) Including lifetime cannabis users

(c) Including current tobacco users

Significant results in bold

Table 2 Baseline differences in pro- and anti-inflammatory biomarkers levels between controls with ≤ 19 and ≥ 25 years of age

Baseline marker	Adolescent group* ($N=24$, mean age: 17.25 ± 2.592) Mean (SD)	Adult group ($N=58$, mean age: 30.12 ± 4.218) Mean (SD)	U	p
Pro-inflammatory and oxidative markers				
NFkB	2.96 (0.436)	3.54 (0.958)	61	0.13
iNOS	97.80 (15.98)	88.69 (20.78)	657	0.82
COX2	95.81 (41.67)	82.88 (34.33)	667	0.89
PGE_2	403.4 (234.39)	254.69 (175 33)	700	0.12
NO^-_2	11.67 (2.09)	13.31 (4.26)	370	0.95
TBARS	1.56 (0.44)	2.30 (1.31)	766	0.28
Anti-inflammatory markers				
IκBα	77.87 (11.78)	98.16 (28.83)	571	0.25
15d -PGJ_2	633.24 (22.24)	612.58 (24.33)	581	0.54
PPARγAct	1.52 (0.71)	1.62 (0.79)	626.5	0.66

*In the adolescent-onset FEP group, age ≤ 19 was used to account for up to 1 year of time between onset of psychotic symptoms (≤ 18) and baseline evaluation

that are not correlated with a generalised oxido/nitrosative damage or with differences in psychopathology scores at least 6 months after first diagnosis.

The pro-inflammatory pathway triggered by the activation of NFkB leads to accumulation of oxidative and nitrosative mediators (NO_2^-, PGE_2) through activation of the coding sequences of inflammatory enzymes (iNOS and cyclooxygenase 2 [COX2]) [35]. In our sample, more marked NFκB pathway activation in adolescent-onset FEP than in adult-onset FEP was not counterbalanced by an increase in compensatory anti-inflammatory activity at baseline nor after 6 months of follow-up. This pro-inflammatory status might contribute to depletion of endogenous antioxidant defences and, therefore, to higher oxidative status and cell damage by membrane lipid peroxidation [36]. In this vein, there is increasing evidence supporting the existence of alterations in NFκB dependent pro-inflammatory pathways at different levels, even in cohorts of psychiatric patients very similar to ours [37]. However, the roles of NFκB should not be oversimplified. NFκB is not only a master orchestrator of the inflammatory response, but also an essential regulatory mediator

Table 3 Baseline and 6-month follow-up: differences in pro- and anti-inflammatory biomarkers between first-episode psychosis with age of onset ≤ 18 and ≥ 25 years and within each age-of-onset group from baseline to follow-up

Marker	Base line								follow-up								Base line VS follow-up			
	Onset ≤ 18			Onset ≥ 25			Inter group*		Onset ≤ 18			Onset ≥ 25			Inter group*		Onset ≤ 18**		Onset ≥ 25**	
	n	Median	IQR	*n*	Median	IQR	*F*	*p*	*n*	Median	IQR	*n*	Median	IQR	*F*	*p*	*F*	*p*	*F*	*p*
Pro-inflammatory and oxidative markers																				
NFκB	13	5.93	2.59	21	3.52	1.99	5.832	**0.024**	20	6.76	32.51	38	4.89	2.38	4.26	**0.044**	0.370	0.554	1.73	0.200
iNOS	22	107.01	32.29	30	161.52	41.53	0.845	0.364	18	127.36	45.43	37	89.64	63.77	1.267	0.266	0.328	0.576	11.43	**0.003**
COX2	21	134.76	145.31	30	114.94	70.56	1.334	0.255	18	143.77	123.52	37	191.10	241.35	3.125	0.083	0.104	0.752	0.247	0.623
PGE_2	25	400.61	274.11	39	265.68	428.42	0.189	0.666	20	842.39	651.13	38	551.04	387.55	4.63	**0.036**	5.59	**0.033**	0.158	0.693
NO^-_2	13	12.80	6.84	22	14.02	9.24	0.656	0.426	20	15.54	13.07	38	20.48	4.41	4.17	**0.046**	7.90	**0.024**	0.039	0.845
TBARS	22	1.70	3.25	38	1.80	2.95	0.604	0.441	20	6.61	2.02	38	4.26	1.92	0.015	0.902	1.97	0.181	0.349	0.559
Anti-inflammatory markers																				
IκBα	22	79.68	86.42	30	70.89	74.76	0.055	0.816	18	71.98	101.49	37	80.46	118.01	0.572	0.453	0.143	0.712	0.050	0.825
15d -PGJ_2	25	551.56	198.52	35	627.27	306.62	1.62	0.210	20	371.31	125.01	38	389.63	219.05	1.52	0.222	0.305	0.591	0.034	0.856
PPARγ	15	0.86	1.48	29	0.79	0.84	0.782	0.383	20	1.11	0.53	38	0.98	0.48	2.84	0.098	0.688	0.421	0.330	0.569

IQR interquartile range

*Non-parametric one-factor ANCOVA, with age-of-onset group as the independent variable and values of pro- and anti-inflammatory markers as the dependent variables. The covariates were days from the first psychotic symptoms until the baseline visit, age of onset of cannabis use, cotinine level, and sex

**Non-parametric repeated-measures mixed-effects model. Timing of evaluation as the independent variable and values of pro- and anti-inflammatory markers as the dependent variables. The covariates were days from the first psychotic symptoms until the baseline visit, age of onset of cannabis use, cotinine level, and sex

Statistically significant results in bold

of cell survival, neuroprotection, neuronal transmission, and plasticity [38].

In our sample, age at onset of cannabis use was lower in adolescent-onset FEP and duration of psychotic symptoms previous to baseline visit was longer in cases with adolescent-onset FEP. None of the remaining clinical characteristics differed significantly between groups. Cannabis use may be related to increased oxidative stress and inflammation in preclinical models [39]. We controlled for these and other potentially related factors such as cotinine level, a proxy for tobacco use [40], in our analyses. All patients included in the study were taking antipsychotic medications, with no differences in the antipsychotic profile by age of onset groups or in daily antipsychotic dose measured as chlorpromazine equivalents. Therefore, the differential alteration of the inflammatory cascade in FEP by age of onset in our study cannot be attributed to disease-independent age-related differences or to the treatment pattern, symptom severity, or functional severity.

Whether inflammatory dysfunction in psychosis has a causal role or if it is the result of a protracted illness and other life circumstances of psychotic patients, including sedentary lifestyle or tobacco consumption [41, 42] is yet to be determined [reviewed in [43]]. There is mounting evidence that levels of inflammatory and oxidative stress markers are higher in people at high risk of psychosis and may predict psychotic conversion [44, 45]. Patients with early psychotic illness show marked neurodevelopmental deviations [46]. Early inflammatory and oxidative stress status may disrupt neurodevelopmental processes, contributing to a longer illness and earlier onset of psychotic symptoms. Although our results do not enable us to establish causation, the fact that patients with earlier development of psychotic symptoms have a more pronounced pro-inflammatory status lends support to the view that cellular and systemic inflammation may contribute to cellular processes that accelerate the onset of psychosis [16].

Oxidative stress imbalance in adolescents with FEP has been correlated with cognitive deficits [47] and decreasing grey matter over time [48], which has been shown to be associated with a poorer clinical prognosis [49]. The fact that inflammation progression is worse in early-onset FEP could also be linked to the cellular profile, which would be in line with reports of poorer clinical prognosis in earlier onset FEP patients [3, 5, 6]. Although we did not find differences in clinical status or general functioning measurements for either age-of-onset group at the start or follow-up point of this study, longer follow-up is warranted to confirm these results and the potential effect of biochemical variables on differential clinical outcomes by age of onset.

Inflammatory changes described in this work are systemic in nature and therefore may be linked to cardiovascular and other systemic clinical outcomes [50, 51]. If patients with earlier onset have more marked systemic inflammation, and are sensitive to metabolic adverse events of psychopharmacological treatments such as weight increase [52] that also affect pro-inflammatory status [53], this group may be especially vulnerable to inflammation-derived systemic outcomes, including higher cardiovascular risk, as observed in this particular clinical setting [54].

A question of special relevance is the need to consider inflammation as a potential treatment target, particularly in early-onset FEP. The fact that patients with adolescent-onset psychosis have increased NFκB at baseline and follow up, with no consequences in anti-inflammatory controlling systems, may suggest a potential better response of adding NSAIDs, coxibs and antioxidants to treatment schedules to control the increase in NFκB-dependent pathways than in the adult-onset group. In chronic psychosis, in contrast, other anti-inflammatory COX-2–regulated pathways also change [55, and reviewed in 43] so NSAIDs, including coxibs, might block COX-dependent anti-inflammatory pathways (15d-PGJ_2 and PPARγ).

Our results may be viewed in light of several limitations. The number of patients enrolled, the attrition rates, and sample quantity (which interfered with our analysis of every parameter in all the samples and caused missing data both at baseline and at follow-up), all point to a possible type II error that could have masked differences between the different age-of-onset groups. We used mixed models to take advantage of their ability to give unbiased results in the presence of random missing data. The design as a case control study did not enable us to establish causation. However, this is the first study to assess differences in inflammation by age of onset in a FEP sample including adolescent- and adult-onset cases, studied with the same methodology.

Adolescent-onset FEP may be characterised by higher pro-inflammatory status than adult-onset FEP. Irrespective of aetiology, it seems reasonable to consider inflammation as a therapeutic target for adolescents with psychosis in the early stages of their illness.

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