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SHORT COMMUNICATION

Chronic low-grade peripheral inflammation is associated with severe nicotine dependence in schizophrenia: results from the national multicentric FACE-SZ cohort

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Abstract Chronic peripheral inflammation (CPI) has been associated with cognitive impairment in schizophrenia (SZ). However, its sources remain unclear, more specifically it is not known whether tobacco smoking is a source of inflammation or not in SZ subjects. Moreover, nicotine (NIC), the major psychoactive compound of tobacco, shows strong anti-inflammatory properties in vitro, as well as inducing a severe biological dependence when administered repeatedly. The objective of the present study was to determine if CPI was associated with tobacco smoking and/or NIC dependence in schizophrenia. Three hundred and forty five stabilized community-dwelling SZ subjects aged 16 years or older (mean age = 32 years, 73% male) were consecutively included in the network of the FondaMental Expert Centers for Schizophrenia and assessed with validated scales. CPI was defined by a highly sensitive C-reactive protein (hsCRP) ≥3 mg/L. Current tobacco status was self-declared. Severe NIC dependence was defined by a Fagerstrom Test for Nicotine Dependence score ≥7. Overall, 159 (46.1%) were non-smokers, 117

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(33.9%) and 69 (20%) were current tobacco smokers with, respectively, low and severe nicotine dependence. In a multivariate model, CPI remained associated with severe NIC dependence (29 vs 15%, OR = 2.8, $p = 0.003$) and body mass index (OR = 1.1, $p < 0.0001$), independently of socio-demographic characteristics and antidepressant intake. No association of CPI with low to moderate tobacco smoking dependence, number of daily smoked cigarettes, cannabis use, alcohol use or illness characteristics was found (all $p > 0.05$). CPI was associated with severe NIC dependence but not with tobacco smoking with low to moderate NIC dependence in SZ, independently of socio-demographic variables, body mass index, alcohol consumption and antidepressant intake. This result highlights the potential CPI consequences of the high prevalence of heavy tobacco smoking in SZ, indicating the importance of new therapeutic strategies for tobacco cessation in SZ.

Keywords Schizophrenia · Nicotine dependence · Tobacco smoking · Inflammation · Antidepressant

Introduction

The contribution of chronic peripheral inflammation (CPI) to schizophrenia (SZ) has received considerable attention in the last decade [1, 2]. In clinical practice, CPI is commonly measured by an elevated blood C-reactive protein (CRP) level [3]. A recent meta-analysis showed abnormally high CRP levels in 28% of SZ patients compared to healthy controls [4], with abnormal CRP levels being recently found to be a risk factor for late-onset SZ [5]. CPI is suspected to be one of the pathophysiological substrates of SZ, being recently associated with cognitive impairment, a significant SZ symptom [6]. A wide body of data shows that the adjunctive use of anti-inflammatory medications are effective in improving SZ symptomatology [7]. Determining the sources of CPI is therefore a significant investigative goal, with the potential to provide new therapeutic strategies for improving clinical and functional outcomes.

The causes of CPI remain unclear in SZ. CPI has been associated with antidepressant consumption and abdominal obesity in SZ patients [8]. Tobacco smoke exposure has been described as a major source of inflammation in non-SZ smokers ([9–13] reviewed in [14]). SZ patients smoke more frequently and more heavily than the general population, as well as in comparison to patients with other psychiatric disorders [15]. However, no association between tobacco smoking and CPI in SZ has been found in recent ecological studies [8, 16, 17].

Among all the molecules in cigarette smoke, nicotine (NIC) is the major psychoactive substance. Moreover, contrary to cigarette smoke as a whole, NIC has shown strong anti-inflammatory properties. NIC is a major activator of the alpha-7 nicotinic acetylcholine receptors (α7 nAChRs) that are highly expressed in systemic and central immune cells [18]. α7 nAChR activation on these cells suppresses proinflammatory processes, as reviewed recently [19, 20]. Such anti-inflammatory effects have been proposed to underlie the improvement in ulcerative colitis symptoms of tobacco smokers, when compared to non-smokers [21]. As NIC also induces biological dependence, which highly predicts the maintenance of tobacco smoking, measures of NIC dependence act as an indirect marker of NIC consumption in tobacco smokers. NIC dependence has been recently associated with inflammation in healthy adolescents [22]. It remains unclear if this association was causal or due to confounders, such as weight, alcohol/cannabis consumption and sex differences. The association between NIC dependence and inflammation has never been explored in SZ to date.

The objective of the present study was therefore to determine if CPI was associated with, respectively, tobacco smoking (cigarette smoke exposure), daily number of smoked cigarettes and/or only with severe NIC dependence, while considering key socio-demographic and clinical relevant confounding factors. Our hypothesis was that CPI was not associated with SZ tobacco smoking [8, 16, 17] and that SZ smokers with severe NIC dependence had lower CPI compared to SZ smokers with low to moderate NIC dependence and SZ non-smokers [19, 20].

Experimental procedures

Study population

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of ten Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles), set up by a scientific cooperation foundation in France, the FondaMental Foundation (http://www.fondation-fondamental.org) and created by the French Ministry of Research to create a platform that links thorough and systematic assessment to research [23].

Inclusion criteria

Consecutive clinically stable patients, as defined by no hospitalization and no treatment changes during the 4 weeks before evaluation [24], aged 16 years or older, with a DSM-IV-TR diagnosis of SZ or schizoaffective disorder were included in this study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centres

network. All participants were referred by their general practitioner or psychiatrist who subsequently received a detailed evaluation report, with suggestions for personalized interventions.

Non-inclusion criteria

Patients with a history of neurological disorders (including stroke, epilepsy and head injury) or all non-psychiatric concurrent illnesses affecting the central nervous system and inflammation (especially auto-immune illnesses, such as lupus and rheumatoid arthritis) were excluded from the present study.

Data collected

Patients were interviewed by members of the specialized multidisciplinary team of the Expert Center. Diagnoses interviews were carried out by a psychiatrist according to the Structured Clinical Interview for Mental Disorders (SCID 1.0) [25]. Information about education, onset and course of the illness, body mass index were recorded. Alcohol and/or cannabis use disorders were defined according to the SCID 1.0. In the present study, the presence of the disorder was defined by the presence of an abuse and/or dependence. According to the SCID 1.0, anyone meeting one or more of the "abuse" criteria within a 12-month period would receive the "abuse" diagnosis. Anyone with three or more of the "dependence" criteria during the same 12-month period would receive a "dependence" diagnosis. The SCID has demonstrated a good reliability [26].

Current tobacco status, age at first cigarette and age at onset of regular tobacco smoking were self-declared by the patient at the time of evaluation. NIC dependence was measured by the Fagerstrom Test for Nicotine Dependence (FTND), the most widely used self-reported measure of NIC dependence [27]. The number of daily smoked cigarettes was reported in the FTND questionnaire and classified in three groups: <10 cigarettes/day, [1, 4, 10–28] cigarettes/day and >30 cigarettes/day (heavy smoking). Severe NIC dependence was defined by a Fagerstrom score ≥7 [27]. The smoking status was defined according the current tobacco status and NIC dependence, and had three values, namely 0 for non-smokers, 1 current smoker with low to moderate NIC dependence (Fagerstrom score <7) and 2 for current smoker with severe NIC dependence (Fagerstrom score ≥7).

Ongoing psychotropic treatments were recorded. As antipsychotics may influence peripheral inflammation [22], compliance into treatment was evaluated by clinicians using the Brief Adherence Rating Scale (BARS). BARS scores range from 0 to 100, 100 being the highest level of compliance (the patient did not forget the treatment intake in the last 30 days).

High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring). CPI was defined as blood CRP level >3 mg/L according to The Emerging Risk Factors Collaboration; 2010. Patients with hs-CRP levels >20 mg/L, which corresponds to an acute inflammation, were not included in the analyses.

Ethical concerns

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, number AU 1143). All data were collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

Statistical analysis

Socio-demographics, clinical characteristics and comorbidities were presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. Univariate associations between demographic and clinical characteristics of SZ subjects with or without CPI were performed using the Chi-square test for categorical variables and the Wilcoxon–Mann–Whitney test for continuous variables.

Multiple logistic regression was performed to assess the association between CPI, smoking status and NIC dependence. Variables with p values <0.20 in univariate analysis (BMI and antidepressant intake) were included in the multivariate regression model to evaluate factors associated with chronic peripheral low-grade inflammation. Age and sex were forced in the final model as confounding factors.

Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL). All statistical tests were two-tailed, with α level set at 0.05.

Results

Overall, 345 SZ subjects enrolled in the FACE-SZ cohort were included in this study. Table 1 shows demographic and clinical characteristics of the sample, as well as the currently administered treatments.

The majority of the sample ($N=252$, 73%) were men, a sample mean age of 32.3 ± 9.8 years old. Mean illness duration was 10.6 ± 8.1 years, with a mean PANSS total score of 70.9 ± 19.1. CPI, as indicated by CRP level, was evident in 110 SZ patients (31.8%).

Table 1 Factors associated with chronic peripheral inflammation (CPI) in 345 community-dwelling schizophrenic subjects: univariate and multivariate analyses

	Whole sample ($n=345$)		Univariate analysis				p	Multivariate analysis			P
			No CPI ($n=235$, 68.1%)		CPI ($n=110$, 31.8%)						
	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%		aOR	95% CI		
Socio-demographic characteristics											
Sex (male), n (%)	252	73.0%	175	74.5%	77	70.0%	0.38	0.80	0.43	1.47	0.47
Age (years) mean (SD)	32.3	9.8	32.2	9.9	32.8	8.6	0.54	0.99	0.96	1.02	0.52
Universitary level***, n (%)	137	42.3%	94	43.1%	43	40.6%	0.66				
Illness characteristics											
Childhood trauma (CTQ score), mean(SD)	41.9	12.2	42.4	12.7	41.8	12.4	0.69				
Age at onset (years), mean (SD)	21.6	6.6	21.6	7.0	21.7	6.7	0.91				
Age at first antipsychotic treatment, mean (SD)	22.9	6.7	23.0	7.2	23.3	6.0	0.75				
Illness duration (years), mean (SD)	10.6	8.1	10.5	8.3	11.1	7.5	0.57				
PANSS positive score, mean (SD)	14.8	5.8	14.9	5.9	15.1	6.1	0.75				
PANSS negative score, mean (SD)	20.6	7.0	21.0	7.3	20.4	6.7	0.48				
PANSS general psychopathology score, mean (SD)	35.6	10.2	36.2	10.6	36.0	9.8	0.86				
PANSS total score, mean (SD)	71.0	19.1	72.1	19.8	71.7	18.3	0.84				
GAF score, mean (SD)	49.1	12.8	49.4	13.6	48.2	13.1	0.44				
Current depressive episode (CDRS score ≥6), n (%)	98	29.0%	28	25.9%	70	30.4	0.39				
Current manic episode (YMRS score ≥12), n (%)	12	3.6%	7	3.1%	5	4.8%	0.45				
Body mass index, mean(SD)	26.1	5.2	25.3	4.5	28.7	5.6	<0.0001	1.13	1.07	1.19	<0.0001
Comorbidities											
No smoking (ref)	159	46.1%	114	48.5%	45	40.9%					
Current smoker with low to moderate nicotine dependence**	117	33.9%	84	35.7%	33	30%		1.25	0.67	2.33	0.48
Current smoker with severe nicotine dependence**	69	20.0%	37	15.7%	32	29.1%	0.022	2.82	1.42	5.63	0.003
Number of daily smoked cigarettes**											
<10 cig/day	46	24.6%	34	18.2%	12	6.4%	0.11				
[10–30] cig/day	120	64.2%	78	41.7%	42	22.5%					
>30 cig/day	21	11.2%	10	5.3%	11	5.9%					
Current alcohol disorder[a], n (%)	20	5.8%	14	6.0%	6	5.5%	0.85				
Current cannabis disorder[a], n (%)	46	13.3%	34	14.5%	12	10.6%	0.37				
Age at regular tobacco smoking onset (years), mean (SD)	17.5	4.8	17.8	5.5	17.5	4.2	0.71				
Age at first cigarette (years), mean (SD)	14.7	3.2	15.0	3.8	14.9	2.4	0.94				
Age at cannabis disorder onset (years), mean (SD)	19.4	3.9	18.6	4.3	21.5	5.0	0.44				
Treatment variables											
Second generation antipsychotic (vs first generation), n (%)	252	87.2%	166	86,0%	86	89.6%	0.39				

Table 1 (continued)

	Whole sample ($n=345$)		Univariate analysis					Multivariate analysis			
			No CPI ($n=235$, 68.1%)		CPI ($n=110$, 31.8%)		p				P
	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%		aOR	95% CI		
Antidepressant, n (%)	97	33.6%	59	30.6%	38	39.6%	0.13	1.03	0.59	1.82	0.91
Adherence (BARS score), mean (SD)	88.1	22.7	86.0	26.6	88.0	21.7	0.54				

CPI was defined by blood highly sensitive C-reactive protein (hs-CRP) blood levels ≥3 mg/L

Mean (SD) mean ± standard deviation, *aOR* adjusted odds ratio, 95%CI: 95% confidence interval, *CTQ* Childhood Trauma Questionnaire, *PANSS* Positive And Negative Symptoms Scale for Schizophrenia. GAF: Global Assessment of Functioning, *CDRS* Calgary Depression Rating Scale for Schizophrenia, *YMRS* Young Mania Rating Scale, *BARS* Brief Adherence Rating Scale

Significant associations are in bold. As the number of daily smoked cigarettes was issued from the Fagerstrom Questionnaire, this data has not been included in the multivariate analysis

[a] As defined in the Structural Clinical Interview for mental Disorders (SCID-1)

**Severe nicotine dependence was defined by a Fagerstrom Test for Nicotine Dependence score >=7

***Universitary level was defined as highschool diploma or higher

Overall, 159 participants (46.1%) were non-smokers, 117 (33.9%) and 69 (20%) were current tobacco smokers with, respectively, low to moderate and severe NIC dependence. The mean age at first cigarette was 14.7 ± 3.5 years and the mean age at regular tobacco smoking onset was 17.6 ± 4.8 years. The mean FTND score was 5.3 ± 2.3. Current cannabis use disorder was evident in 46 patients (13.3%), and current alcohol use disorder in 20 patients (5.8%).

The results of univariate and multivariate analyses are presented in Table 1. In the univariate analyses, CPI was significantly associated with smoking status ($p=0.022$) and body mass index ($p<0.0001$) but not with number of daily smoked cigarettes, cannabis or alcohol disorders, history of childhood trauma nor with antidepressant intake (all $p>0.05$).

In the multivariate analyses, CPI was significantly higher in current smoker with severe NIC dependence than in non-smokers (OR = 2.824; 95% CI 1.416–5.633, $p=0.003$) but CPI was not significantly different between current smoker with low to moderate NIC dependence and non-smokers (OR = 1.25; 95% CI 0.671–2.34, $p=0.48$), independent of socio-demographic characteristics and antidepressant intake. CPI was also significantly higher in severe NIC dependence than in low to moderate NIC dependence (OR = 2.26; 95% CI 1.11–4.59, $p=0.025$). Body mass index remained significantly associated with CPI (OR = 1.13; 95% CI 1.07–1.19, $p<0.0001$).

Discussion

Our major findings may be summarized as follows: in a large non-selected community-dwelling sample of SZ patients, CPI is positively associated with NIC dependence and body mass index, independent of the assessed potential confounding factors. No association of CPI with low to moderate tobacco smoking neither dependence, nor cannabis use or alcohol disorders were found in the present study.

The prevalence of CPI in our sample (31%) was comparable with the global prevalence of abnormal CRP levels found in a SZ meta-analysis by Miller et al. (28%) [4]. Overall, 37% of SZ smokers reported severe NIC dependence in the present study. This rate is comparable to the 41% reported in another recent French study [28]. This suggests that our community-dwelling multi-centric sample may be representative of SZ patients. Age at illness onset and sex ratio also suggest that the present sample may be representative of patients with schizophrenia. However, the present results should be replicated in different SZ population (for example in younger populations).

In the present study, a positive association between CPI and severe NIC dependence has been found. This is a new

result, as this association has never been explored in previous studies. This finding is not consistent with our initial hypothesis that NIC dependence would be associated with lower CPI due to the in vitro anti-inflammatory effects of NIC [19, 20]. Due to the cross-sectional design of this study, a causal relationship cannot be drawn. However, given that elevated peripheral CRP levels positively correlated with the severity of positive symptoms in a recent meta-analysis [1], the present results may support the self-medication hypothesis of tobacco smoking in SZ, which has produced considerable controversy [29–32]. As such, SZ smokers with CPI may self-administer NIC to limit the negative effects of CPI. Other hypotheses may be proposed, including genetic shared vulnerability between CPI and NIC dependence, which has been described in other psychiatric illnesses [33]. Substantial evidence from preclinical, as well as recent clinical, studies indicate that 7 nAChR deregulation may account for some of the cognitive and affective symptoms of SZ, with NIC use representing a strategy to lessen these symptoms [34]. Further studies should also determine if CPI at baseline is associated with an increase rate of tobacco use relapse in tobacco cessation programs, and if NIC substitutes administration may improve peripheral inflammation in SZ patients. As CPI and NIC dependence have both been associated with cognitive impairment in SZ [6, 35], it remains also to be determined if inflammation mediates the association between cognitive impairment and NIC dependence in SZ smokers.

No association between age at regular tobacco smoking onset and age at first cigarette with peripheral inflammation has been found in the present results. A memory bias cannot be excluded. However, as current smoking status and number of daily smoked cigarettes have not been associated with peripheral low-grade inflammation in the present study, this may suggest that NIC dependence is specifically associated with peripheral low-grade inflammation.

An association between CPI and body mass index was also found in the present study, which is consistent with previous findings [8, 36–39]. Adipose tissue is not only specialized in the storage and mobilization of lipids, but can also function as an endocrine organ releasing numerous cytokines, including proinflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α). In obesity, macrophage infiltration into adipose tissue [40] as well as decreased adiponectin can contribute to the inflammatory profile evident in abdominally obese patients [41]. Although highly significant, this association was mild in the present results. Measuring abdominal perimeter appears as a better estimation of perivisceral fat [42] and seems recommended in future studies exploring the association between inflammation and abdominal obesity.

Altogether, the present results suggest that CPI may be associated with NIC dependence in SZ subjects. It may therefore be reasonably suggested that improving inflammatory disturbances may alleviate NIC dependence in this population. SZ is still associated with a mean loss of life expectancy of 10–20 years [43]. Both CPI and NIC dependence/heavy tobacco smoking have been suggested as important risk factors for shortened life expectancy. Improving both inflammation and NIC dependence may therefore be a major health challenge in the care of SZ people.

Limits Due to the cross-sectional design of our study, it was not possible to conclude to a causal relationship between CPI and NIC dependence. Exercise, diet and gut permeability have been suggested as risks factors for peripheral inflammation [44] and have not been explored in the present study. As the measurement of other proinflammatory markers is not recommended in French daily practice, other inflammatory markers, such as IL-6 and TNF⟨, were not included in our study. Carbon monoxide dosage has not been carried out in the present study, although it may have improved tobacco consumption assessment [45, 46]. In France, this method is mostly used in tobacco cessation program and pulmonary disease departments and has not been implemented in the Schizophrenia Expert Center Network to date. NIC dependence was measured by the FTND score, which include the number of daily smoked cigarettes. Only FTND total score has been used for the present study. Further studies should explore if chronic peripheral inflammation is associated with the amount of daily smoked cigarette and/or with the craving/desire to smoke. The number of subjects with hs-CRP >20 mg/L has not been recorded. Exploring the association between chronic peripheral inflammation and NIC dependence in this population seems recommended for future studies.

Strengths The studies using the FTND questionnaire for NIC dependence assessment in SZ are currently few in number, with the association between CPI and NIC dependence having never been explored to date. The use of homogenous and exhaustive standardized diagnostic protocols across the centers and inclusion of a large number of potential confounding factors in the multivariate analysis (socio-demographic variables, psychotic and mood symptomatology, treatments, adherence into treatment, history of childhood trauma and cannabis and alcohol disorders) may also be mentioned in the strengths of the present work.

Conclusion

CPI is associated with severe NIC dependence in SZ smokers. Future studies should determine if anti-inflammatory strategies may alleviate NIC dependence in this population.

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Compliance with ethical standards

Conflict of interest None.

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