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Guillaume Fond, O. Godin, L. Boyer, F. Berna, M. Andrianarisoa, N. Coulon, L. Brunel, E. Bulzacka, Bruno Aouizerate, D. Capdevielle, et al.

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**Chronic low-grade peripheral inflammation is associated with ultra resistant schizophrenia. Results from the FACE-SZ cohort.**

**SHORT COMMUNICATION**

Running title: peripheral inflammation is associated with ultraresistant schizophrenia

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**Abstract**

*Introduction.* A high rate of patients with schizophrenia (SZ) does not sufficiently respond to antipsychotic medication, which is associated with relapses and poor outcomes. Chronic peripheral inflammation has been repeatedly associated with schizophrenia risk and particularly to poor responders to treatment as usual with cognitive impairment in SZ subjects. The objective of present study was to confirm if ultra resistance to treatment in schizophrenia (UTRS) was associated to chronic peripheral inflammation in a non-selected sample of community-dwelling outpatients with schizophrenia.

*Methods.* Participants were consecutively included in the network of the FondaMental Expert Centers for Schizophrenia and received a thorough clinical assessment, including recording of current treatment. Current psychotic symptomatology was evaluated by the Positive and Negative Syndrome scale for Schizophrenia (PANSS). UTRS was defined by current clozapine treatment+ PANSS total score $\geq$ 70. Functioning was evaluated by the Global Assessment of Functioning scale. High sensitivity CRP (hs-CRP) was measured for each participant as a proxy to define peripheral low-grade inflammation.

*Results.* 609 stabilized community-dwelling SZ subjects (mean age=32.5 years, 73.6% male gender) have been included. 60(9.9%) patients were classified in the UTRS group. In multivariate analyses, UTRS has been associated independently with

chronic peripheral inflammation (OR=2.6 [1.2-5.7], p=0.01), illness duration (OR=1.1 [1.0-1.2], p=0.02) and impaired functioning (OR = 0.9 [0.9-0.9], p=0.0002) after adjustment for age, sex, current daily tobacco smoking, metabolic syndrome and antidepressant consumption.

Conclusion. Peripheral low-grade inflammation is associated with UTRS. Future studies should explore if anti-inflammatory strategies are effective in UTRS with chronic low-grade peripheral inflammation.

Keywords: resistant schizophrenia, inflammation, functioning

## **Introduction**

For most affected individuals, schizophrenia (SZ) is a chronic and disabling disorder. One of the most important predictors of relapse in schizophrenia is the response to antipsychotic medication, known to be highly variable in schizophrenia. The definition of treatment resistance remains controversial in spite of its importance ((Howes et al., 2017a), for review see (Peuskens, 1999)). One in three patients is classified as treatment-resistant schizophrenia (Lindenmayer et al., 2009; Meltzer, 1997). Clozapine is still considered to date as the most effective antipsychotic (Sultan et al., 2017) and a meta-analysis confirmed the largest effect size among the newer generation antipsychotics (Leucht et al., 2013). Since the pivotal study by Kane et al. (Kane et al., 1988) found that about a third of stringently defined treatment-resistant patients responded to clozapine, it has been the gold standard medication in this specific population and is now recommended in international therapeutic guidelines (Abidi et al., 2017; Hasan et al., 2015, 2013; Howes et al., 2017b; Keating et al., 2017; Leucht et al., 2015; Lo et al., 2016; Remington et al., 2017; Samalin et al., 2013; Stahl et al., 2013). However, 40% still remain classified as resistant to clozapine, which has been called “ultra resistance to treatment in schizophrenia” (UTRS) (Siskind et al., 2017). The pathophysiological bases of UTRS remain largely to be elucidated (Suzuki et al., 2011).

Among the factors associated with resistance to antipsychotics, chronic low-grade peripheral inflammation has received increased interest during the last decade (Fond et al., 2015; Khandaker et al., 2015). Inflammatory blood markers have been recently shown to predict poor treatment response to antipsychotics ((Fernandez-Egea et al., 2016; Mondelli et al., 2015; Nishimon et al., 2017), for review see (Fond et al., 2015)). In clinical practice, peripheral low-grade inflammation is measured by an elevated blood level of highly sensitive C-reactive protein (hs-CRP) (Lopresti et al., 2014). CRP is a common final denominator in the inflammation cascade (Lopresti et al., 2014) and has been associated with increased SZ risk in recent meta-analyses (Fernandes et al., 2016; Inoshita et al., 2016). High blood CRP level has also been associated with cognitive impairment, a major source of disability in schizophrenia (Bulzacka et al., 2016), and a large set of data has confirmed that anti-inflammatory add-on strategies are effective in improving SZ symptomatology (Fond et al., 2014;

Nitta et al., 2013; Sommer et al., 2013). If UTRS is associated with peripheral low-grade inflammation, it may be reasonably hypothesized that anti-inflammatory strategies should be useful to improve the outcomes of this specific population.

The objectives of the present study were to determine the prevalence of UTRS in a large non-selected sample of stabilized community-dwelling SZ outpatients, and to determine whether UTRS was associated with peripheral low-grade inflammation.

## **Population and methods**

### *Study design*

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 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 ([www.fondation-fondamental.org](http://www.fondation-fondamental.org)) and pioneered by the French Ministry of Research in order to create a platform that links thorough and systematic assessment to research (Schürhoff et al., 2015).

### *Study population*

Consecutive clinically stable patients (defined by no hospitalization and no treatment changes during the 4 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder were consecutively included in the study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centres network. All subjects were referred by their general practitioner or psychiatrist who subsequently received a detailed evaluation report with suggestions for personalized interventions.

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 on-going and treated inflammatory disorder such as lupus, rheumatoid arthritis or acute infectious disorder were not included in 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 two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0). Information about education, onset and course of the illness, body mass index and comorbidities were recorded.

Schizophrenic symptomatology was assessed using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Current depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDRS) (Addington et al., 1993). This scale was specifically designed to identify specific depressive symptomatology that cannot be related to negative symptoms of schizophrenia. Manic symptoms were evaluated using the Young Mania Rating Scale (YMRS) (Young et al., 1978). Daily global functioning was evaluated with the Global Assessment of Functioning Scale (GAF) (Startup et al., 2002). Ongoing psychotropic treatment was recorded. Alcohol and/or cannabis disorders were defined according to the SCID 1.0. Self-reported adherence to pharmacological treatment was evaluated using the French translation of the MARS (Misdrahi et al., 2004).

#### *UTRS definition*

UTRS was defined by current clozapine treatment and a mean PANSS score  $\geq 70$ , which is suggested to correspond to “moderately to severely ill” patients (Leucht et al., 2005).

#### *Measurements*

A blood draw for routine blood exam was performed and triglycerides, LDL, HDL and total cholesterol as well as glucose (if patients confirmed fasting for at least 10h) were collected. High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring) blinded to schizophrenia status. Abnormal CRP level was defined as  $>3$  mg/L (Emerging Risk Factors Collaboration et al., 2010).

#### *Metabolic syndrome (MetS) definition*

Sitting blood pressure (BP) and anthropometrical measurements were recorded in the Expert Centers. Two BP measurements were made 30 seconds apart in the



right arm after the participant had sat and rested for at least 5 minutes. A third BP measurement was made only when the first two BP readings differed by more than 10 mm Hg. The average of the two closest readings was used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. This was performed with a tape equipped with a spring-loaded mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was collected for metabolic profiles analysis. Fasting levels of serum triglyceride (TG) and fasting plasma glucose were measured by an automated system, and serum high-density lipoprotein cholesterol (HDL-C) level was measured by electrophoresis. The diagnosis of metabolic syndrome was defined according to the modified criteria of the International Diabetes Federation (IDF) (Alberti et al., 2006), which requires the presence of three or more of the following five criteria: high waist circumference ( $>94$  cm for men and  $>80$  cm for women), hypertriglyceridemia ( $\geq 1.7$  mM or on lipid lowering medication), low HDL cholesterol level ( $<1.03$  mM in men and  $< 1.29$  mM in women), high blood pressure ( $\geq 130/85$  mmHg or on antihypertensive medication), high fasting glucose concentration ( $\geq 5.6$  mM or on glucose-lowering medication).

#### *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, January 18th, 2010). 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 and clinical characteristics and treatments are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data were examined for normal distribution with the Shapiro-Wilk test and for homogeneity of variance with the Levene test. Comparisons between ultra

resistant and non-ultra resistant individuals regarding demographic, clinical characteristics were performed using the chi-square test for categorical variables. Continuous variables were analysed with Student t-tests for normally distributed data and in case of normality violation, additional Mann-Whitney tests were performed to confirm the result.

Variables with P values < 0.20 in univariate analysis were included in the multivariate logistic regression model of factors associated with ultra resistant schizophrenia. Sex and age were forced into the final model as confounding factors. This study was a confirmatory analysis. No correction for multiple testing has therefore been carried out, which is consistent with recommendations (Bender and Lange, 2001). Analyses were conducted using SAS (release 9.3; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed, with  $\alpha$  level set at 0.05.

## Results

609 stabilized community-dwelling SZ subjects (mean age=32.5 years, 73.6% male gender) have been included. Overall, 60(9.9%) patients were classified in the UTRS group (table 1). UTRS has been significantly associated with positive, negative and cognitive scores (all  $p < 0.0001$ ), with excitement score ( $p = 0.003$ ) but not with depressive score ( $p = 0.08$ ). Compared to non-UTRS, patients of the UTRS group were found to have higher illness duration (13.0 vs. 10.6 years,  $p = 0.01$ ), more frequently paranoid delusion (56.9% vs 53.1%,  $p = 0.002$ ), grandiosity delusion (23.4% vs. 10.6%,  $p = 0.009$ ), mystic delusion (23.1% vs. 11.7%,  $p = 0.02$ ), auditory hallucinations ( $p = 0.02$ ) and disorganized behavior (43.9% vs. 25.2%,  $p = 0.005$ ). No difference on catatonia, somatic delusion, guilty delusion, erotomania, jealousy delusion, reference delusion, visual and cenesthetic hallucinations, avolia, alogia and blunted affect has been found (all  $p > 0.05$ ). In the present study, no significant difference of hs-CRP levels has been found between the subgroup of clozapine-treated non-UTRS group and UTRS group (all being administered clozapine by definition) (44.4% vs. 46.3%,  $p = 0.88$ ).

In multivariate analyses, UTRS has been associated independently with chronic peripheral inflammation (OR=2.6 [1.2-5.7],  $p = 0.01$ ), impaired functioning

(OR = 0.9 [0.91-0.97],  $p=0.0002$ ) and illness duration (OR= 1.1 [1.0-1.2],  $p=0.02$ ) after adjustment for age, sex, current daily tobacco smoking, metabolic syndrome and antidepressant consumption. The mean CRP levels in UTRS and non-UTRS groups were presented in figure 1. 45 patients (8.2%) received clozapine treatment without being ultra treatment resistant. No difference of clozapine blood levels has been found between UTRS and no UTRS groups (mean 523.7 mg/mL (sd=320) in clozapine non-remitters vs. 460.0 (sd=380.7) in clozapine remitters,  $p=0.56$ ). Antipsychotic consumption was not included in the multivariate model because it was not significantly associated with UTRS in univariate analysis. However, forcing antipsychotic consumption in the model did not change the results (hsCRP OR =2.1 [1.0-4.2],  $p=0.04$ ).

## **Discussion**

Our major findings may be summarized as follows: in a large non-selected community-dwelling sample of 609 SZ subjects, UTRS has been identified in almost 10% of the subjects and was independently associated with chronic peripheral inflammation and impaired functioning.

Almost 10% of our sample has been identified as UTRS. This is consistent with previous data mentioned in the rationale, which have suggested that one third of the patient were treatment resistant and 40% of them (=12%) were ultra-resistant (Siskind et al., 2017).

UTRS has been associated with impaired functioning in the present study. This result confirms the clinical significance of our definition of resistance into treatment. UTRS has been extensively suggested as a separate schizophrenia subtype and has been associated with a specifically impaired functioning ((Iasevoli et al., 2016), for review see (Strassnig and Harvey, 2014)).

UTRS has been shown to be associated with peripheral inflammation for the first time in the present study. Some previous studies have yielded indirect clues suggesting that abnormal inflammatory markers may predict treatment non-response in schizophrenia (Mondelli et al., 2015; Nishimon et al., 2017). Moreover, electroconvulsive therapy, a treatment that has shown effectiveness in resistant schizophrenia, has recently shown to modify peripheral inflammatory markers

(Kartalci et al., 2016). However, a previous study found no association between peripheral inflammation and resistant SZ as defined by clozapine initiation or hospital admission due to schizophrenia after having received at least 2 prior antipsychotic monotherapy trials of adequate duration) (Horsdal et al., 2017). This discrepancy in the results is probably due to the discrepancy between definitions, the present study focusing on ultra-resistant SZ and not resistant SZ only.

Ultra-resistance has been associated with illness duration, which is consistent with the results of previous studies supporting the staging model (Ortiz et al., 2017).

Altogether, the present results combined with literature data suggest that anti-inflammatory strategies may be useful in UTRS. Celecoxib has been the most studied anti-inflammatory add-on agent in SZ (Sommer et al., 2013). Some trials are ongoing to determine if aspirin, N-acetyl-cysteine, minocycline and omega 3 fatty acids may be useful anti-inflammatory add-on strategies for this specific population (Cuéllar-Barboza et al., 2017; Fond et al., 2014; Rossell et al., 2016).

*Limits.* These results should be taken with caution. As our study has a cross-sectional design, no causal link can be definitely inferred. Exercise, diet and gut permeability have been suggested as risk factors for peripheral inflammation (Berk et al., 2013) and have not been explored in the present study, as well as hormonal contraception, omega 3 fatty acid or vitamin D consumption (that may alleviate inflammation). As the dosage of the other markers of inflammation is not recommended in daily practice in France, other inflammatory markers (including interleukin IL-6 and Tumor Necrosis Factor TNF $\alpha$ ) were not measured in our study. Our sample may not be representative of all patients with schizophrenia, particularly because institutionalized; hospitalized or very handicapped patients (making thorough assessment difficult) were not referred to the expert centers. HsCRP was the only inflammatory marker in the present study. Given that clozapine has been described to have immunomodulatory effects (Pollmächer et al., 1996), these results should be confirmed with other markers like IL-6 and TNF-alpha. However, no association between clozapine and increased CRP has been found in the present study.

*Strengths.* 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, adherence to treatment, addictive behaviors) may be mentioned in the strengths of the present work. In the end, our national multi-centric sample of SZ patients referred to the Expert Centers may be underscored as another strength.

*Conclusion.* UTRS is independently associated with peripheral low-grade inflammation in stabilized SZ community-dwelling subjects. Future studies should explore if anti-inflammatory add-on strategies are effective in UTRS.

#### Contributors

GF and LB performed the statistical analysis. GF, LB, FS and ML wrote the first complete manuscript. GF, LB, FS and ML edited earlier versions of the manuscript for important intellectual content. All authors were involved in the patients' recruitment, the clinical evaluation, acquisition of the clinical data, modified the manuscript and approved the final version.

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**Conflicts of interest**

None declared.

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