Psychiatric and psychological follow-up of undergraduate and postgraduate medical students: prevalence and associated factors. Results from the national BOURBON study. Running title: mental health and addictive behavior of medical students

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Inflammatory DEpression Advances in Schizophrenia (IDEAS): a precision medicine approach of the national FACE-SZ cohort.

Running title: inflammatory depression in schizophrenia

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Abstract

Background. Major Depressive Disorder (MDD) is a therapeutic challenge in schizophrenia (SZ). Untangling different forms of MDD appears as the best current strategy to improve remission to treatment in the so-called precision medicine approach.

Aims. The objectives of the present study were to determine (i) the prevalence of Inflammatory Depression (ID) in stabilized SZ outpatients (ii) if ID was associated with clinical or cognitive profiles that may help clinicians detecting ID (iii) if antidepressants were effective in ID and (iv) the biological correlates of ID that may orientate personalized treatments.

Method. Participants were consecutively included and received a thorough 2 days-clinical assessment.

Results. 785 subjects were recruited in the FACE-SZ cohort. 289 (36.8%) were diagnosed with MDD (remitted or unremitted), of them 57 with ID (19.7%). No clinical or cognitive features were associated with ID (all $p>0.05$). ID has been associated with increased abdominal perimeter (aOR=4.48, p=0.002) and latent Toxoplasma infection (aOR=2.19, p=0.04). While antidepressants were associated with decreased depressive symptoms level in ID, 44% of the subjects remained unremitted under antidepressant, with no association with CRP blood levels.

Conclusions. ID may not differ from other forms of depression by its clinical symptoms but by its aetiologies. ID is associated with increased perivisceral fat and latent Toxoplasma infection that are both potentially related to gut/microbiota disturbances. Specific anti-inflammatory drugs and microbiota-targeted therapeutics appear as promising strategies in the treatment of inflammatory depression in schizophrenia.

Declaration of interest. None.

Keywords: depression, inflammation, schizophrenia, adiposity, Toxoplasma

Introduction

Detecting and treating major depressive disorder remains a therapeutic challenge in schizophrenia (SZ). Recent studies have shown that stabilized SZ outpatients have high rates of major depression, with poor antidepressant administration and high treatment-resistance rates (Guillaume Fond et al., 2018). The last decade has shown that chronic low-grade peripheral inflammation plays a major role in depression onset and maintenance (Valkanova et al., 2013). In schizophrenia, peripheral inflammation has been specifically associated with depressive symptoms (Faugere et al., 2018) and antidepressant consumption (Fond et al., 2016). However, it remains unclear if inflammatory depression (ID) differs from non-inflammatory depression (NID) in SZ subjects, from a clinical and biological point of view. Inflammation has been also associated with SZ cognitive impairment (Bulzacka et al., 2016) in increased suicide risk in general population and depressive disorders ((Batty et al., 2018; Cáceda et al., 2018) for review see (Brundin et al., 2015)). The following sources of inflammation have been identified in both general population and psychiatric samples: addictions (tobacco smoking, alcohol and cannabis consumption), history of childhood trauma, overweight, sleep disorders and lack of physical activity (for review see (Berk et al., 2013)). Psychotropic drugs may influence inflammatory status. In non-SZ subjects, Selective Serotonin Reuptake inhibitors (SSRI) have shown anti-inflammatory properties (Hannestad et al., 2011) while tricyclic have been associated with higher inflammation in SZ subjects (Fond et al., 2017). Antipsychotic drugs may also have differential effects on peripheral inflammation (Fond et al., 2017).

The objectives of the present study were to determine (i) the prevalence of Inflammatory Depression (ID) in stabilized SZ outpatients (ii) if ID was associated with clinical or cognitive profiles that may help clinicians detecting ID (iii) if antidepressants were effective in ID and (iv) the biological correlates of ID that may orientate personalized treatments.

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) 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 8 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.

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).

ID definition

Depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDRS (Addington et al., 1992; Lançon et al., 2000)). A score ≥6 is considered as a current major depressive episode. The CDRS is the most widely used scale for assessing depression in SZ. It has excellent psychometric properties, internal consistency, inter-rater reliability, sensitivity, specificity, and discriminant and convergent validity (Addington et al., 1992). Non-remitted MDD was defined by current antidepressant treatment (unchanged for more than 8 weeks) and current Calgary score≥6 (Guillaume Fond et al., 2018).

Chronic peripheral low-grade inflammation was defined by a High sensitivity CRP (hs-CRP) ≥3 mg/L (Fond et al., 2016) and was measured with an assay using nephelometry (Dade Behring) blinded to schizophrenia status.

Sociodemographic, clinical, treatments and biological variables

The clinical scales, metabolic data and cognitive tests have been previously comprehensively described (Schürhoff et al., 2015) and are available in supplementary material. As the clinical evaluation and the biological analyses were separated in time and location, the clinical evaluation and the biological analyses were both blinded.

Solid phase-enzyme microplate immunoassay methods were used to measure IgG class of antibodies to T. *gondii* in blood sample. The results were quantified by calculating a ratio between the reactivity of the samples and a standard sample run on each microplate. Latent Toxoplasma infection was defined by T. *gondii* IgG ratio ≥0.8, equivalent to ≥10 international units. All samples were analysed under code by the laboratory not having access to diagnostic or clinical information.

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, clinical characteristics, addictive behaviour, treatments, biological variables and cognition 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 respectively ID and NID regarding demographic, clinical and biological variables 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 analysis (PANSS disorganized factor, clozapine treatment, tricyclic and Norepinephrine antidepressants, triglyceride disturbance, glycaemic disturbance, increased abdominal perimeter and latent Toxoplasma Infection). Age and gender were forced. The final models included odds ratios and 95 % confidence intervals. 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 SPSS 17.0 software (SPSS Inc., Chicago, IL). All statistical tests were two-tailed, with α level set at 0.05.

Results

785 subjects recruited in the FACE-SZ cohort were included in the present study. 289 (36.8%) were diagnosed with MDD (remitted or unremitted), 57 with ID (19.7%) (flow chart figure 1).

Clinical, cognitive, addictive, biological and treatment characteristics of ID subjects are presented in table 1. ID patients were not found to differ from the others by their clinical or cognitive profile. In the multivariate model, ID has been associated with increased abdominal perimeter (aOR=4.48[1.73-11.60], p=0.002) and latent Toxoplasma infection (aOR=2.19[1.02-4.73], p=0.04) compared to non-ID after adjustment for age, gender, disorganization, clozapine and antidepressants administration and other metabolic disturbances.

Antidepressants were found to be associated with lower depressive symptoms level in both ID and non-ID subjects after adjustment for age, gender and hsCRP blood levels (respectively aOR=0.62[0.44-0.89], p=0.009 and aOR= 0.78[0.71-0.86], p<0.0001). CRP blood levels were not found to differ between antidepressant-treated and untreated subjects and between remitters and non-remitters (all p>0.05).

Discussion

The present findings may be summarized as follows: ID was identified in almost one on five SZ patients with major depression. ID subjects were found to have

increased abdominal perimeter and higher frequency of latent Toxoplasma infection after adjustment for confounding variables. Antidepressants were effective in ID subjects however around 44% of them remained unremitted under conventional treatment.

We found no association between ID and lifestyle (sleep disorders, physical activity) but a strong association with body mass index and abdominal perimeter. It should be underlined that diet has not been explored to date in the FACE-SZ cohort due to a lack of validated diet questionnaire in French psychiatric populations. Diet may strongly influence both intra-abdominal fat and depression and should be explored in the future. Increased abdominal perimeter is a marker of intra-abdominal fat and has been associated with depressive symptoms in non-SZ populations (Everson-Rose et al., 2009; Klakk et al., 2018; Remigio-Baker et al., 2014) and with both white and gray matter brain abnormalities (Kharabian Masouleh et al., 2018, 2016; Zhang et al., 2018). There is now multiple evidence for a bidirectional relationship between depression and increased adiposity, with overweight/obesity being associated with an increased prevalence of depression, and in turn, depression augmenting the risk of weight gain and obesity (for review see (Capuron et al., 2017)). Hypothalamic-pituitary-adrenal (HPA) axis activation occurs in the state of stress; concurrently, the HPA axis is also dysregulated in obesity and metabolic syndrome, making it the most well-understood shared common pathophysiological pathway with depression (Lee et al., 2016). Numerous studies have investigated the effects of different classes of antidepressants on body weight. Previous clinical studies suggest that the tricyclics amitriptyline, nortriptyline and imipramine, and the serotonin norepinephrine reuptake inhibitor mirtazapine are associated with weight gain. Despite the fact that selective serotonin reuptake inhibitor (SSRI) use has been associated with weight loss during acute treatment, a number of studies have shown that SSRIs may be associated with long-term risk of weight gain; however, because of high variability and multiple confounds in clinical studies, the long-term effect of SSRI treatment and SSRI exposure on body weight remains unclear (for review see (Lee et al., 2016)). An animal paradigm has shown that the combination of stress and antidepressants followed by long-term high-fat diet results, long after discontinuation of antidepressant treatment, in markedly increased weight, in excess of what is caused by high-fat diet alone (Lee et al., 2016).

Altogether, these results suggest that reducing abdominal fat should be a priority in the ID treatment in SZ patients.

The present findings found no difference between inflammatory and non-inflammatory depression in regard of cognitive function. This is probably due to the fact that no association of impaired cognition and depression has been found in the FACE-SZ cohort, while inflammation has been associated with cognitive impairment (Bulzacka et al., 2016). Future studies should explore the specific mechanisms of cognitive impairment in schizophrenia (that are probably multiple), that seems to be associated in part with chronic-low grade peripheral inflammation but not with major depression.

ID has been associated with latent Toxoplasma infection for the first time in the present study. Toxoplasma *gondii* is an apicomplexan protozoan intracellular parasite with a widespread distribution in both developed and developing countries. Toxoplasma has been extensively associated with schizophrenia onset risk in the general population (for meta-analysis see (Sutterland et al., 2015)) and has been identified as a major source of inflammation in SZ subjects (G. Fond et al., 2018). While our meta-analysis published in 2015 did not confirm an association between Toxoplasma and major depression (Sutterland et al., 2015), new conflicting results on the associations between Toxoplasma and depression have been published (Alvarado-Esquivel et al., 2016; Gale et al., 2016; Suvisaari et al., 2017). A new meta-analysis is warranted to explore the links between Toxoplasma, depression and inflammation. Much of the attention relating to the role of Toxoplasma infection in neuropsychiatric disorders has focused on the brain, where Toxoplasma tissue cysts can persist for extended periods of time. However, recent discoveries relating to the role of the gastrointestinal tract in cognition and behavior suggest that Toxoplasma may also increase susceptibility to human brain diseases through immune activation, particularly involving the gastrointestinal mucosa (for review see (Severance et al., 2016)).

To make a long story short, these two potential etiological tracks for ID onset in schizophrenia seem to converge on the gastrointestinal track. The so-called "psychomicrobiotic" currently appears as one of the most promising strategies to improve psychiatric treatments (for review see (G. Fond et al., 2015)).

The higher rates of second-line treatments (clozapine and tricyclic agents) may explain the absence of difference of depressive symptoms severity / effectiveness

of antidepressants between ID and non-ID. Moreover, this absence highlights the need to develop reliable biomarkers to orientate treatments in psychiatry (Guillaume Fond et al., 2015). While alcohol use disorder has been associated with ID in non-SZ population (Archer et al., 2018), this association has not been replicated in the present sample. This may be due to the low rate of alcohol use disorder in our population and should be explored in SZ populations with higher frequency of alcohol use disorders. We found no association between childhood trauma and ID, which is consistent with a recent study carried out in non-SZ population (Mackinnon et al., 2018). A meta-analysis should determine if childhood adversity is associated with increased risk of inflammation in adulthood.

Strengths. The FACE-SZ cohort is unique by its sample size and longitudinal studies are needed to determine depression trajectories in SZ patients.

Limits. In addition to the above-mentioned limits, race/ethnicity has not been reported due to ethical issues. Leptin and inflammatory cytokines (IL-6, IL-1, TNF alpha) should be added in future studies to improve the ID signature (Milaneschi et al., 2017). The Toxoplasma strain and Toxo IgG serointensity have not been measured, as they are not validated in routine clinical practice. There is still a debate on the pro-inflammatory or anti-inflammatory properties of tricyclic agents that should be further explored (Fond et al., 2016; Hannestad et al., 2011; Köhler et al., 2018). Genetic disposition to inflammation may also influence antidepressant response (Zwicker et al., 2018).

Perspectives. Diet, microbiota disturbances, gut permeability, hypovitaminosis D have not been explored in the present study and should be targeted in future studies exploring ID in schizophrenia. Anti-inflammatory, in particular, the administration of anticytokines, including the monoclonal antibody against TNF-α, infliximab, may represent a useful strategy for the treatment of ID in schizophrenia (Capuron et al., 2017).

Conclusion

ID may not differ from other forms of depression but these differences may have been erased by ID patients being administered more aggressive antipsychotic and antidepressant medications. The present results suggest that ID may differ not by clinical symptoms but by its etiologies: ID has been associated with both intra-abdominal fat and latent Toxoplasma infection, two tracks that encourage researchers

to explore the gut-brain axis to develop effective treatments in a precision medicine approach.

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Conflicts of interest

None declared.

Contributors

GF and LB performed the statistical analysis. GF wrote the first complete manuscript. GF, LB and PML 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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