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IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology

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ABSTRACT

Objective: The role of inflammation in psychopathology has received great attention over the past decades. Immune system dysfunction and altered cytokine levels have been reported in most psychiatric disorders in adults. Few data are available regarding children and adolescents (C&A), or regarding the relationship between cytokine levels and psychosocial stress.

This study investigates the profile of the most described cytokines in a sample of C&A inpatients affected by an acute psychiatric condition requiring hospitalization, in comparison with healthy subjects, as well as possible associations between psychosocial stressors and psychopathology and/or cytokine concentrations.

Methods: Patients with a diagnosis of Affective, Anxiety, Adjustment, Psychotic, Obsessive–Compulsive, Tic or Tourette Disorders were consecutively recruited from our clinic between June 2010 and February 2012. Controls were recruited from the same geographic area. All subjects were between 8 and 17 years old. Twelve cytokines are compared: interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IFN-γ-induced protein-10 (IP-10), monocyte chemoattractant protein (MCP)-1. Psychosocial stress was measured through the Stressful Life Events Scale, Child and Parents versions (SLES-C and SLES-P) and the evaluation of the family integrity.

Results: One hundred and eleven subjects (77C&A inpatients and 34 healthy controls), of which 54 were males (49%), with a median (interquartile range) age of 16 (13.7–17.3) years, were included in this study. IL-1β, IL6, IL8, IP-10, MCP-1 and monocytes were found to be significantly higher in the patient group ($p < 0.05$). Differences were confirmed when adjusting by BMI, age, gender and drug intake at admission for all cytokines except MCP-1. IL-8 and IL-1β were also higher throughout the different diagnostic categories, than in control group ($p < 0.05$). Stress measures were higher in patients. A significant correlation was found between stress measured by the SLES and some inflammatory markers: SLES_C with IL-1β, IL-8, MCP-1, and SLES_P with IL-1β and monocytes absolute and relative counts (Spearman's r between 0.219 and 0.297, $p < 0.05$).

Logistic regression identified the following variables as independent predictors of the patient condition, (odds ratio per quartile, *p*-value): IL8 (1, 0.9, 12.1, 32.0, $p = 0.044$), IP10 (1, 14.1, 2.5, 3.7, $p = 0.044$), monocyte absolute count (1, 1.1, 6.0, 19.4, $p = 0.030$).

Conclusions: Results show elevated inflammation markers from the innate immune system across C&A acute psychiatric diagnosis, and suggest a link between psychopathology, inflammation and stress. Inflammatory markers resulted predictors of patient status. These exploratory results are coherent with current psychoneuroimmunology and neurodevelopmental investigations.

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1. Introduction

Over the past decades there has been a great interest in the role of inflammation in psychiatric psychopathology. All major psychiatric disorders have been investigated. Recent meta-analysis have been published for schizophrenia and psychotic disorder (SCZ), bipolar disorder (BAD), major depression (MDD), post-traumatic-stress-disorder (PTSD), autism spectrum disorder (ASD) (Miller et al., 2011a; Modabbernia et al., 2013; Gray and Bloch, 2012; Masi et al., 2014; Dowlati et al., 2010) as have some revisions on PTSD (Wieck et al., 2014), and they all conclude that cytokine alterations and a pro-inflammatory state are associated with the disorder in question.

Even though studies have mostly been developed separately for each diagnosis, some findings are common. When summarizing the results across the diagnostic spectrum, it is clear that cytokines such as IL-1β, IL-6, IL-8 and TNF-α, have proven to be higher across various adult patient populations, in comparison with healthy controls (HC). An overview chart is provided in Appendix A of Supplementary information. Of note is the fact that, these cytokines are all suggestive of an inflammation pattern related to innate immunity and monocyte activity, and some authors have posited that this condition may be associated with an activation of the microglia at a central level (Bergink et al., 2014).

It may be noteworthy that most studies analysed a very restricted panel of cytokines: this can give the false impression of a very specific immune activation. To obtain a better picture of the pattern of inflammatory changes, a broad range of immune markers should be investigated and compared throughout all experimental groups.

In order to better understand correlations and possible pathogenic mechanisms, a deeper knowledge of inflammatory and cytokine states in child and adolescent (C&A) psychiatric population is of special interest. This would allow the bypass of the confounding burden of long-term treatment and physical comorbidities often found in adults, and also the optimization of signal detection, because of shorter illness duration and minor allostatic load (Mitchell and Goldstein, 2014) in these subjects.

Literature in C&A psychiatric patients, though increasing, is still limited and heterogeneous. Even though results have been somewhat inconsistent, a recent review (Mitchell and Goldstein, 2014) suggests that there would be preliminary evidence for elevated inflammatory markers also in this population, with some markers such as IL-1β and IL-6 found altered through various disorders.

The presence of common markers across psychiatric disorders is coherent both with clinical observations, and with the most recent findings in genetics and neuroscience. Inputs in favour of a cross-diagnostic approach in psychiatry come from various fields. There is accumulating evidence from genetic studies suggesting shared susceptibility across traditional diagnostic categories in psychiatry: family studies have shown how there is a cross-diagnostic familiar risk for schizophrenia, mood disorders, ASD and attention deficit and hyperactivity disorder (ADHD) (Doherty and Owen, 2014), i.e. how members of families of patients with one disorder, also have a higher risk for the other disorders. Genetic studies also evidence how the same risk-markers, like single-nucleotide-polymorphism (SNP) and copy number variants (CNVs) that have been associated with one specific disorder, can be linked to other disorders as well (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). From a clinical point of view, it is commonly experienced that many symptoms and signs overlap between disorders, and that patients often present with features of more than one disorder, which can account for the high comorbidity observed in psychiatry. This implies that at least some of the underlying biology may not be specific, or at least not at the level of current diagnoses (Doherty and Owen, 2014).

It has been discussed to what extent the overlap across diagnoses, and the lack of specific biomarkers for psychiatric disorders, has to do with a diagnostic classification system that is artificial in many aspects, and that includes patients that are highly heterogeneous (Kapur et al., 2012) under the same diagnostic group.

In the last decades, research has been focusing on new possible ways for classifying mental disorders, relating more specifically to neurobiological substrates, response to treatment, and clinical evolution. In this light also stands the Research Domain Criteria (RDoC) Project, an initiative set up by the National Institute of Mental Health, to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures" (Insel, 2014; Doherty and Owen, 2014).

The same studies show the limits of genetics and the importance of the environment in determining epigenetic variables, and investigators speculate about how the same genetic risk factor can translate into different clinical phenotypes, or into healthy individuals, depending on the interaction with different environments. One of the environmental factors that is currently of interest is childhood trauma and stress. Accumulating evidence, in fact, suggests how adversities and trauma during childhood can be associated with the development of psychiatric disorders with an inflammatory phenotype, both during childhood and later in adulthood (Miller and Cole, 2012; Danese et al., 2008; Dennison et al., 2012).

2. Aims of the study

The current study is grounded on these premises.

As primary objectives, it aims to find possible common or specific markers of inflammation (cytokines) in a population of recently admitted, acutely ill psychiatric young inpatients. It compares the profile of the cytokines most often associated with an acute psychiatric condition, between our study population and a group of healthy subjects, in the search for transdiagnostic markers. Another dimension that has been investigated is the stress level that subjects had undergone, and the possible correlation between stress levels and inflammation parameters.

As a secondary and exploratory objective, it aims to investigate cytokine distribution across the different psychiatric diagnostic clusters.

3. Material and methods

3.1. Subjects

All patients between 8 and 17 years of age admitted to the Acute Child and Adolescent Psychiatry Inpatient Unit of Hospital Clínic of Barcelona, with a diagnosis of Affective, Anxiety, Adjustment, Psychotic, Obsessive–Compulsive, Tic or Tourette Disorders, according to DSM-IV TR Criteria, between June 2010 and February 2012, were invited to participate in the study.

Controls were healthy community subjects within the same age range, who had not received a previous psychiatric diagnosis, and should not score clinically in the psychiatric semi-structured interview (K-SADS-PL) for any psychiatric disorder, except for ADHD. They were recruited from local paediatric and family medicine practices in Hospital Clínicís referral area, among patients social network and through local advertisement. Exclusion criteria for all subjects included an IQ below 80 and an acute or chronic medical condition other than the psychiatric one, as well as regular medication intake, including anti-inflammatory drugs. This cross sectional study was approved by the Ethics Committee of the Hospital Clínic and all parents or legal guardians gave written informed consent before the study began.