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Evidence for increased immune mobilization in First Episode Psychosis compared with the prodromal stage in males

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ABSTRACT

The aim of the study was to gauge both the immune and neuroendocrine function in Ultra High Risk for psychosis (UHR) subjects and compare them with a cohort presenting with First Episode Psychosis (FEP).

We recruited two groups, the first group consisted of 12 UHR males and the second of 25 males with FEP. We measured serum cortisol levels at 08:00, 12:00, 18:00 with their Area Under Curve with respect to the ground (AUCg) and the increase (AUCi) and we measured serum cytokines levels, Interleukin-1a, IL-1a, IL-2, IL-4,IL-5,IL-6,IL-8, IL-10,IL-12, IL-17a, Tumor Necrosis Factor-a (TNF-a), Interferon-γ (IFN-γ). Dexamethasone Suppression Test (DST) was also performed .

The results suggest higher levels of both pro-inflammatory (TNF-a, IL-2, IL-12, IFN-γ) and anti-inflammatory (IL-10) cytokines in the FEP group compared with the UHR counterparts. Regarding the HPA axis function, the prodromal subjects showed a trend for higher AUCg and AUCi change/decrease cortisol levels. On the contrary, the DST results did not differ between the groups. No significant associations were demonstrated within each group among cytokines, cortisol and psychopathology.

The findings favor a hypothesis of a relatively increased mobilization of both the pro- and anti-inflammatory cytokine networks, in FEP compared with that of UHR subjects.

1. Introduction

The neural diathesis-stress model (Walker and Diforio, 1997) of psychosis has been a widely used model to explain the neurobiological basis of the vulnerability the psychotic patients demonstrate to different stressors. Thus, research has focused on the Hypothalamus-Pituitary-Adrenal (HPA) axis function which is known to mediate the organism's response to stressful stimuli so as homeostasis and psychosomatic equilibrium to be maintained (Chrousos, 2000).

Recent research to elucidate the causes of stress vulnerability in psychosis, has involved the study of the HPA axis function in cohorts presented with First Episode Psychosis (FEP), as this group eliminates confounders such as medication and chronicity. The evidence from this approach favors an up regulation of basal cortisol secretion in individuals with FEP vs Healthy Controls (HC). In contrast, the reactive capacity of the HPA axis function and its relation to specific psychopathology remain vague (Karanikas et al., 2014). In addition, there is similar evidence for up regulation of cortisol secretion even prior to the emergence of a full blown psychotic episode, that being at prodrome (Karanikas and Garyfallos, 2015). Indeed, the psychotic prodromal period is characterized by the emergence of a constellation of sub threshold psychotic-like symptoms and progressive functional decline that can precede the onset of an Axis I psychotic disorder. Preliminary evidence suggests a pattern where cortisol levels in At Genetic Risk of Psychosis cohorts tended to be numerically intermediate between the patients group (established psychosis) and the HC (Spelman et al.,2007; Yildirim et al., 2011) . Similarly to the evidence coming from FEP studies, cortisol's fluctuation and reactivity to different stressors in Ultra High Risk of psychosis (UHR) subjects compared with HC, remain vague due to the minimal literature and divergent results (Karanikas and Garyfallos, 2015).

A similar obscurity characterizes the findings in relation to the immune abnormalities in psychosis. The first attempts to review the studies evaluating circulating cytokines produced conflicting

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results (Drzyzga et al., 2006; Potvin et al., 2008; Miller et al., 2011). Heterogeneity appeared to be a common denominator in these studies. This heterogeneity related to differences in diagnoses, setting, medication, phase of illness, comorbidity. The hypotheses referring to the immune aetiopathological backround in psychosis involve i. the macrophage-T Lymphocyte theory (Smith and Maes, 1995), ii. the T helper type 2 shift (Müller and Schwarz, 2010), iii. the microglia activation (Monji et al., 2009), iv. the tryptophane metabolism-kynourenine pathway and astrocyte activation (Müller et al., 2011), v. the synchronous activation of both pro- and anti- inflammatory arms of immunity (Drexhage et al., 2011).

This present study constitutes a preliminary attempt to capture the immune and HPA axis function profile in 2 cohorts, whose clinical presentation lied in close proximity to the emergence of psychosis. The first group incorporated FEP patients and the other UHR subjects. The HPA axis function was investigated in a way to capture evidence not only for the total secretion of cortisol but also its fluctuation throughout time. Plus HPA axis' reactivity/suppressor capacity was gauged with the implementation of the Dexamethasone Suppression Test (DST). In addition, a group of cytokines alleged to serve different immune functions (innate vs adaptive, pro- vs-anti- inflammatory arms) were evaluated. As mentioned before, the data regarding the immune and neuroendocrine profile in the FEP and the prodromal state are minimal and to an extent contradictory.

To our knowledge this is the first study involving a direct comparison of cytokines profile and HPA axis function between the prodrome and the FEP. Given the evidence that inflammation may underlie the aetiopathogenetic substrate of psychosis, we tested the hypothesis that the FEP group (where full blown psychosis becomes clinically evident) would demonstrate increased immune mobilization as well as increased cortisol secretion and/or fluctuation and more blunted cortisol suppression on the DST compared with the UHR group (where the psychotic symptomatology is clinically demonstrated in a more attenuated fashion) .

2. Methods

2.1. Subjects

The study was conducted, from May 2012 up until May 2014, within the settings of two psychiatric clinics; the Psychiatric Department of the 424 General Military Hospital of Thessaloniki and the 2nd Psychiatric Department of Aristotle University of Thessaloniki, located at the Psychiatric Hospital of Thessaloniki, Greece.

The recruitment of the FEP group involved 25 male patients with their first presentation of psychotic episode without affective features. We recruited participants having received a diagnosis of Brief Psychotic disorder or Schizophreniform disorder or Schizophrenia or Psychotic disorder Not Otherwise Specified according to the DSM IV-TR. Drug induced psychosis was excluded, based on the history, clinical presentation and urine drug test. Both the FEP group and the UHR group ($N=12$ males) consisted of military personnel who were referred to the Psychiatric Department of the 424 General Military Hospital of Thessaloniki, Greece for further evaluation of their change/deterioration in their behavior and/or function in their military duties.

2.2. Clinical assessment

2.2.1. Clinical diagnoses

The referred subjects (military male personnel) were clinically evaluated by two psychiatrists (EK, GG) not being the principal treating doctors of the patients. Diagnoses of FEP patients were confirmed with the application of the Structured Clinical Interview (SCID) (First et al., 2002) for DSM-IV-TR. Regarding the UHR group, their recruitment was based on the PACE criteria (Yung et al., 1998) using the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005). According to the pre mentioned classification, UHR individuals must meet at least one of the following constellations of criteria: (a) Attenuated Psychotic Symptoms (APS); denoting the experience of sub threshold positive psychotic symptoms during the past year; (b) Brief Limited Intermittent Psychotic Symptoms(BLIPS); the experience of episodes of frank psychotic symptoms that have not lasted longer than a week and have been self-remitting; or (c) Trait and State Risk Factor; having a first degree relative with a psychotic disorder or the identified subject has been diagnosed with Schizotypal Personality Disorder (SPD) plus a significant decrease in functioning during the previous year. No subjects were diagnosed with any other comorbid psychiatric state.

2.2.2. Psychopathology severity

The symptom severity in both the FEP and UHR groups was assessed with the Greek version (Lykouras et al., 1994) of the Structured Clinical Interview for the PANSS (Kay et al., 1987) and was performed by two psychiatrists (EK, GG) on the same day or within the next two days of blood sampling. The results were calculated as Positive Factor (PANSS PF), Negative Factor (PANSS NF), General Psychopathology (PANSS GP) and Total score (PANSS TOTAL).

2.3. Other inclusion-exclusion criteria

We included FEP subjects who were medication naïve or minimally treated; the later meaning that, depending on their clinical presentation they should not have been for more than 3 days on any type of psychotropic medication (antipsychotic, mood stabilizer, antidepressant, benzodiazepines) up until all blood sampling had been completed. In this way the least possible exposure to the effects of medication was ensured. The UHR participants needed to be drug naïve to be included in the study.

Our study groups consisted of participants between the age group of 18–40, with BMI < 30. Also the design of the study required the participants to be physically healthy with no signs of active inflammation for at least 15 days prior to the study-based on the medical history, physical clinical examination and laboratory investigations.

We excluded subjects with intellectual disability, shift workers and illicit drug use based on history and urine drug tests both at their admission in hospital and prior to that at random sampling according to the practices of the Greek Armed Forces. Participants with any chronic medical state (including but not restricted to impaired thyroid function, polydipsia, asthma, diabetes, chronic fatigue, autoimmune disorders) or medication that could impair the immunological, endocrinological or neurological status were excluded.

All participants gave their informed consent after a thorough explanation was provided regarding the process. The local ethical scientific committees of the two involved hospitals, plus the scientific committee of the Headquarters of the Greek Armed Forces gave their consent for the study. The study was performed in accordance with the last edition of the Declaration of Helsinki.

2.4. Blood collection and analyses

The blood samples were collected within the first 3 days of admission for both the FEP and the UHR subjects. The day 1 of blood sampling, samples were collected at 3 separate points in time; 08:00 morning, 12:00 midday and 18:00 noon. At 23:00 of the first day, 1 mg of Dexamethasone (Dex), was given. At day 2,