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Short Communication

TITLE: “Cytokines, cortisol and IGF-1 in First Episode Psychosis and Ultra High Risk males. Evidence for TNF-α, IFN-γ, TNF-β, IL-4 deviation.”

Short title: Immune alterations in psychosis

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ABSTRACT

The aim of the study was to determine circulating cytokines, cortisol and Insulin-like Growth Factor (IGF)-1, known for their involvement in inflammation, in male patients with First Episode Psychosis (FEP) and subjects at Ultra High Risk (UHR) for Psychosis. The FEP group presented increased pro-inflammatory cytokines (TNF-α, IFN-γ, TNF-β) as well as increased anti-inflammatory cytokine (IL-4) compared with Healthy Controls (HC). The UHR group showed increased IL-4 against HC. In contrast, none of the groups did show deviation from normality in either cortisol or IGF-1 levels. These preliminary findings support the cytokines’ role in the inflammatory hypothesis in psychosis.

Keywords: Cortisol, Cytokines, First Episode Psychosis, IGF-1, Ultra High Risk

1. Introduction

In recent years, the interest of the scientific community in the detection and validation of potential biomarkers regarding the diagnostic validity, prediction of outcome and delineation of causative mechanisms in psychosis, has been increasing. The research that is relevant to the investigation of the inflammatory substrate in psychosis involves the evaluation of immune cells, neurotrophic factors and stress hormones. Respectively, cytokines, Insulin like Growth Factor (IGF)-1 and cortisol have attracted the bulk of the attention lately. Reviews of the circulating cytokines (Drzyzga et al., 2006) and Hypothalamo-Pituitary-Adrenal (HPA) axis function (Bradley and Dinan, 2010) in chronic medicated patients with psychosis, posed
heterogeneity in demographic and clinical factors as the explanation for the inconclusive results. Thus, reviews of studies on cytokines (Upthegrove et al., 2014) and cortisol in First Episode Psychosis (FEP) (Karanikas et al., 2014) and Ultra High Risk (UHR) (Karanikas and Garyfallos, 2015) for psychosis subjects emerged, suggesting a number of theories (Drexhage et al., 2011; Müller and Schwarz, 2010; Smith and Maes, 1995), regarding the immune alterations as well as upregulation of cortisol secretion proximal to the full blown FEP. In regard to IGF-1, albeit its known neuroprotective and antiapoptotic properties (Dore et al., 1997), the evidence for its role in psychosis remains controversial (Palomino et al., 2013; Venkatasubramanian et al., 2010). Furthermore, research has hinted at the interplay among IGF-1, cortisol and cytokines; IGF-1 levels could be influenced by cortisol (Cianfarani et al., 1998), pro-inflammatory cytokines could activate the HPA axis and glucocorticoids inhibit the pro-inflammatory cytokines’ secretion (Chrousos, 2000). To our knowledge no study has incorporated the simultaneous evaluation of these parameters in FEP and UHR states. Thus, we aimed to test the hypothesis for increased pro-inflammatory cytokines ([IL-1, IL-6, Tumor Necrosis Factor-α, TNF, of the innate immunity], (Interferon-γ, IFN, IL-2, IL-8, IL-12p70, TNF-β of the T helper-1, Th-1, immune response of the adaptive immunity]) and decreased anti-inflammatory ones (IL-4, IL-5, IL-6, IL-10 of the Th-2 immune response of the adaptive immunity), as well as increased cortisol and decreased IGF-1 in serum of male FEP patients compared to Healthy Controls (HC). We also attempted to validate the presumption of deviation from normality of those factors in a cohort at UHR state.

2. Methods

2.1. Subjects

The study was conducted from May 2012 up until May 2014, within the setting of the Psychiatric Department of the 424 General Military Hospital of Thessaloniki, Greece. The recruitment of the FEP group involved 25 male patients with their first presentation of psychotic episode without affective features. 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 for further evaluation of their change/deterioration in their behavior and/or function. In addition, we included 23 male volunteer participants, coming from the Hospital’s staff, as HC.

2.2. Clinical assessment

2.2.1. Clinical Diagnoses

FEP was defined as the presence of daily psychotic symptoms longer than a week according to the Melbourne group’s Personal Assessment and Crisis Evaluation (PACE) Criteria (Yung et al., 1998). Diagnoses of the FEP patients were confirmed with the application of the Structured Clinical Interview (SCID) for DSM-IV-TR (First et al., 2002). Regarding the UHR group, their recruitment was based on the PACE criteria 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 subject was diagnosed with comorbid psychiatric states. Finally, psychiatric morbidity was excluded within the HC subjects (SCID-Non Patient) and it was confirmed that they did not have any first degree relatives diagnosed with psychosis. All diagnoses were performed by 2 qualified senior psychiatrists (E.K. and E.N.), subject to comprehensive training and inter rater reliability testing ($\kappa = 0.9$).

2.2.2. Psychopathology severity

We assessed symptom severity in FEP and UHR patients with the Greek version of the Positive and Negative Syndrome Scale (PANSS) (Lykouras et al., 1994). The results were calculated as PANSS Positive Factor (PF), Negative Factor (NF), General Psychopathology (GP) and Total score (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. The UHR participants needed to be drug naïve to be included in the study.

All the participants were 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. They were aged between 18-40, with BMI<30, without intellectual disability, neither shift work. Any illicit psychotropic drug users were excluded; this was ensured through history taking and urine drug tests. 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 as well.

All participants gave informed consent. The study was approved by the local ethical committee of the hospital and performed in accordance with the latest edition of the Declaration of Helsinki.

2.4. Blood Analyses
The day 1 of blood sampling, samples were collected at 3 separate points in time; 08:00, 12:00 and 18:00. Cortisol was measured from the 3 samples at day 1 with Radioimmunoassay using the DIA source CORTISOL-RIA-CT Kit manufactured by DIA source ImmunoAssays S.A. Rue du Bosquet, 2, B-1348 Louvain-la-Neuve, Belgium. The cytokines were measured based on the principles of Fluorescent Bead Immunoassay and the Flow Cytomix. The kits used were the Flowcytomix Human Th1/Th2 11plexKit (IFN-γ, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-α, TNF-β) BMS 810FF and the Flow Cytomix BMS 82017FF human IL-17A simplex kit of the Bender MedSystems GmbH Campus Vienna Biocenter2, A-1030 Vienna, Austria. The method used for the IGF-1 evaluation involved the Eliza Immunoassay and the kit was the Mediagnost IGF-I-ELISA E20, Germany. The manufacturers’ instructions were followed. Serum for measurement of both IGF-1 and cytokines was collected from day 1 at 08:00, thawed, stored and measured simultaneously.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 20 software. The cortisol values were assessed with the formula of ‘Area Under Curve with respect to ground’ (cort-AUCg) (Pruessner et al., 2003). All cytokine and IGF-1 values were logarithmically transformed. Multi-group differences were assessed by way of the Kruskal-Wallis test, individual group differences against the HC were assessed by way of Mann-Whitney tests with the p value corrected for multiple comparisons using the Bonferroni correction, target p set at <0.025 for an alpha of <0.05. Intra-group correlations were assessed with the Spearman r, statistic.

3. Results

Groups’ demographics and clinical data are presented in Table 1. Four FEP group patients were diagnosed with Brief Psychotic Disorder, 16 with Schizophreniform Disorder and 4 with Psychotic Disorder Not Otherwise Specified. The mean (±SD) Duration of their Untreated Psychosis (DUP) was estimated to be 14.8(±6.3) weeks. Similarly, 8 UHR individuals presented with APS, 2 with BLIPS and 2 were diagnosed with SPD plus functional deterioration during the past year. Eight (32%) out of 25 FEP patients were under treatment (risperidone, olanzapine, quetiapine, haloperidol) for a mean of 1.75±0.8 days. The mean daily Chlorpromazine equivalent dose was 555.3±388 mg. All the UHR subjects were drug naïve. The demographic parameters, shown in Table 1, did not differ significantly among the groups (all p>0.05) and along with the medication and DUP parameters of the FEP only group, did not correlate with the cortisol levels nor with the cytokines and IGF-1 levels (all p>0.05); thus they were not controlled as confounders.

The FEP group showed significantly higher concentrations of TNF-α (z=-2.374, p=0.018), TNF-β (z=-2.379, p=0.018), IFN-γ (z=-2.343, p=0.020), IL-4 (z=-2.552, p=0.011) compared with the HC group. The UHR group exhibited a significant increase of IL-4 compared with the HC group (z=-2.591, p=0.010), Figure 1.
Within the FEP group, TNF-α positively correlated with IFN-γ (rho=+0.76, p<0.001) and IL-4 (rho=+0.58, p=0.002) and similarly IFN-γ with IL-4 (rho=+0.72, p<0.001). Within the UHR group, IL-4 was not associated with the rest of cytokines. No significant correlations (all p>0.05) were demonstrated among the cytokines, IGF-1, cort-AUCg and psychopathology within each of the FEP and UHR groups.

4. Discussion

The FEP group showed significantly increased levels of serum TNF-α, TNF-β, IFN-γ and IL-4 levels compared to HC, thus suggesting activation of different branches of immunity with the emergence of full blown psychosis. The UHR group presented increased IL-4 levels against the HC, confirming the presumption of immune alterations even from the prodromal stage. The results concerning the HPA axis function, showed that neither the FEP nor the UHR group did reach a significant deviation from the HC. Finally, none of the FEP and UHR groups did show significant change in serum IGF-1 levels compared with the HC.

The increased levels of TNF-α and IFN-γ in our FEP group, lie in partial agreement with both Miller et al.’s (2011) meta-analysis which attributed to them a trait marker role and Upthegrove et al.’s (2014) meta-analysis of drug naive FEP studies which suggested high effect size for elevated TNF-α but not for IFN-γ. The deviation of TNF-α along with cytokines from the Th-1 immune response of the adaptive immunity, such as IFN-γ and TNF-β, in our FEP group, could imply the activation of a pro-inflammatory process, thus confirming our testing hypothesis, which stands congruent with the Smith and Maes’s (1995) theory of a synchronous activation of the innate and Th-1 response of the adaptive arm of immunity in psychosis. This presumption is further supported by the significant positive associations between TNF-α (innate immunity) and IFN-γ (Th-1 cytokine of the adaptive arm) shown only by our FEP group. Notably, our study suggests a significant role for another pro-inflammatory cytokine, TNF-β, whose role in psychosis has hitherto minimally been investigated.

Regarding IL-4, its concentration was increased in the FEP group compared with the HC. This finding lies against our initial hypothesis. Interestingly, IL-4 was the only cytokine exhibiting increased levels in the UHR group in relation to the HC. Consequently, a mobilization of IL-4 in serum in both the FEP and UHR groups could be speculated. This increase of IL-4 could possibly be explained by its role in the activation of the Th-2 immune response and its consequent anti-inflammatory action. Conversely viewing, the increased IL-4 levels in both the FEP and UHR groups against HC, could be interpreted as etiological factor instead of compensatory neuroprotective state. In that case, Müller and Schwarz’s (2010) aetiopathogenetic hypothesis of a Th-2 shift could be substantiated. Unfortunately, the cross sectional design of the study did not allow evaluation of the conversion ratio of the UHR subjects to psychotic patients, thus precluding any firm conclusions about the role of IL-4’s increase in relation to the etiological substrate, pathophysiological sequence,
Contrary to our prediction, neither the FEP group nor the UHR subjects did exhibit clear evidence for cortisol increase in relation to the HC. This finding appears to deviate from the speculation of an up regulation of cortisol secretion during FEP (Karanikas et al., 2014) and even earlier at prodrome (Karanikas and Garyfallos, 2015). Yet, despite the fact that our groups were matched for gender, age, BMI, smoking, education—which was not the case for the majority of the reviewed studies—plus they were only minimally exposed to medication; the sample size was small and the diagnoses provisional and subject to change prospectively. The later reflects the diverse pathways from ‘genome to the phenome’, which in turn may relate to the phenotypic, pathophysiologic and etiological heterogeneity of psychosis (Nasrallah et al., 2011). Should an inadequacy/deficit of the HPA axis function to change/adapt to the increase of the pro-inflammatory cytokines of both the innate (TNF-α) and the adaptive (IFN-γ, TNF-β) immunity arms, is the case in our FEP patients, as evidenced by the non-deviation of circulating cortisol, then a deficit of the stress system to preserve homoeostasis could be speculated. Again, it is premature to hypothesize whether this non deviation of the HPA axis function as well as our findings regarding the circulating cytokines’ levels, constitute a link to etiology or on the chain of pathophysiology, are compensatory, a consequence, or an epiphenomenon.

Finally, the non-deviation of IGF-1 in the FEP cohort of the present study lies in agreement with other studies (Palomino et al., 2013) but contrasts others which either support decrease (Venkatasubramanian et al., 2010) or increase (Lee and Kim, 2007) of circulating IGF-1 in patients with psychosis compared with HC. The discrepancy of the results among the aforementioned studies (ours included) could be attributed to the heterogeneity of the participant groups in terms of diagnoses [Schizophrenia alone (Lee and Kim, 2007; Venkatasubramanian et al., 2010) vs mixed Schizophrenia and Bipolar Disorder (Palomino et al., 2013) vs newly diagnosed FEP with only 1 Schizophrenia subject (ours)], medication status [naïve (Venkatasubramanian et al., 2010) vs combination of naïve and medication free for 4 weeks (Lee and Kim, 2007) vs combination of naïve and minimally treated (ours)] as well as BMI and physical activity. To our knowledge this is the first study involving the evaluation of IGF-1 in UHR subjects.

Collectively, our findings of a clear deviation in the circulating TNF-α, TNF-β, IFN-γ, IL-4 of the FEP group and IL-4 of the UHR group from the HC, as opposed to the insignificant alteration to either cortisol or IGF-1 levels, provide another piece of evidence to the conundrum relating to the underlying pathophysiological mechanisms in psychosis as early as in FEP and UHR states. Yet, the findings should be interpreted with caution as they are not informative of their causality directions. Consequently, the authors acknowledge the need for more studies with longitudinal design and larger cohorts.

Authors Contributions
The Authors have equally contributed to the study conception and design, acquisition of data or analysis and interpretation of data, data collection, drafting the article, writing of the manuscript; All Authors approve of the content.

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Statement of conflicts of interests: none

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REFERENCES


Figure 1.
Mean of logarithmically transformed cytokines’ concentrations within the groups. IL: Interleukin; IFN: Interferon; TNF: Tumor Necrosis Factor; FEP: First Episode Psychosis; UHR: Ultra High Risk; HC: Healthy Control.
Table 1. Legend

UHR: Ultra High Risk for Psychosis; FEP: First Episode Psychosis; HC: Healthy Controls; Age, Education in years; BMI: body mass index; PANSS: Positive and Negative Syndrome Scale; PF: Positive Factor; NF: Negative Factor; GP: General Psychopathology; TOTAL: Total score; IL: Interleukin; IFN: Interferon; TNF: Tumor Necrosis Factor; IGF: Insulin-like Growth Factor; cort-AUCg: cortisol Area Under Curve with respect to ground; Variables presented in mean (SD); only cytokines and IGF in median (25%, 75% percentile). Cytokines levels in pg/ml, IGF-1 in ng/ml, cort-AUCg in μg/dl/min. Age, Education, BMI analyzed with one way ANOVA; smoking with χ²; Cytokines, IGF-1 and cort-AUCg with Mann-Whitney tests with the p value corrected for multiple comparisons using the Bonferroni correction; *: target p set at <0.025 for an alpha of <0.05; (a): FEP vs HC; (b): UHR vs HC, IL-6 and IL-17A levels were under detection limits in >50% cases (data not shown).

Table 1. Group demographics and clinical data—cytokines, IGF-1, cortisol levels
<table>
<thead>
<tr>
<th>Demographics</th>
<th>HC(n=23)</th>
<th>UHR (n=12)</th>
<th>FEP(n=25)</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.04 (2.9)</td>
<td>24.5 (3.1)</td>
<td>25.48 (5.4)</td>
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<td>Education</td>
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<td>13.16 (2.1)</td>
<td>12.44 (1.8)</td>
<td>.307</td>
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<tr>
<td>BMI</td>
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<td>24.15 (1.9)</td>
<td>24.8 (4.2)</td>
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<tr>
<td>Smoking(Yes\No)</td>
<td>7/16</td>
<td>7/5</td>
<td>14/25</td>
<td>.138</td>
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<tr>
<td>Clinical Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS PF</td>
<td>4.92 (9.06)</td>
<td>18.64 (4.7)</td>
<td>&lt;.001</td>
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<tr>
<td>PANSS NF</td>
<td>5.33 (9.78)</td>
<td>18.4 (4.2)</td>
<td>.001</td>
<td></td>
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<tr>
<td>PANSS GP</td>
<td>8.92 (16.27)</td>
<td>35.36 (5.37)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>PANSS TOTAL</td>
<td>19.17 (34.75)</td>
<td>72.8 (11.2)</td>
<td>.001</td>
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</tr>
<tr>
<td>Clinical Data</td>
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<td></td>
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<tr>
<td>IL-1β</td>
<td>68(44.82)</td>
<td>64 (40.67)</td>
<td>51(39,117)</td>
<td>.959(a), .258(b)</td>
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<tr>
<td>IL-2</td>
<td>97(93,101)</td>
<td>95 (94,97)</td>
<td>99(96,121)</td>
<td>.065(a), .702(b)</td>
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<td>IL-4</td>
<td>68(68,70)</td>
<td>71(70,71)</td>
<td>71(69,76)</td>
<td>.011(a*),.010(b*)</td>
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<td>IL-5</td>
<td>3.4(4, 4.5.9)</td>
<td>.4 (.4,3.8)</td>
<td>11.5(4,5.3)</td>
<td>.702(a), .172(b)</td>
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<tr>
<td>IL-8</td>
<td>381(125,1168)</td>
<td>331 (0.2,1028)</td>
<td>218(35,694)</td>
<td>.287(a), .402(b)</td>
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<td>IL-10</td>
<td>10(3,36)</td>
<td>6 (1,7)</td>
<td>19(4,55)</td>
<td>.287(a), .115(b)</td>
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<td>IL-12p70</td>
<td>12(11,17)</td>
<td>11 (10,12)</td>
<td>14(11,23)</td>
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<td>IFN-γ</td>
<td>22(16,36)</td>
<td>20 (17,27)</td>
<td>39(23,122)</td>
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<td>TNF-α</td>
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<td>.8(8.8)</td>
<td>9(8.6,9.4)</td>
<td>.018(a*), .276(b)</td>
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<td>.6(6.6)</td>
<td>.6(6.6)</td>
<td>.017(a*), .252(b)</td>
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<td>IGF-1</td>
<td>5.56 (5.37, 5.72)</td>
<td>5.68 (5.4, 6.02)</td>
<td>5.57 (5.29, 5.84)</td>
<td>.82(a), .259(b)</td>
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<td>Cort-AUCg</td>
<td>165.33 (54.56)</td>
<td>206.4(72.85)</td>
<td>170.44(61.91)</td>
<td>.934(a), .071(b)</td>
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