Asian Journal of Psychiatry 25 (2017) 219–223

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

An exploratory study of immune markers in acute and transient psychosis☆

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ARTICLE INFO

Article history:
Received 19 June 2016
Received in revised form 22 November 2016
Accepted 22 November 2016

Keywords:
Acute and transient psychotic disorders
Stress
Brief psychiatric rating scale
Hypothalamic-pituitary-adrenal (HPA) axis
Interleukin (IL)-6
Tumour Necrosis Factor (TNF)-α
Transforming Growth Factor (TGF)-β
Cortisol

ABSTRACT

The aim of this study was to look into the balance of pro-inflammatory (TNF-α, IL-6) and anti-inflammatory (TGF-β) cytokines and their association with stress, alterations in HPA axis activity and the disease severity in acute psychosis.

Socio-demographic and clinical details were collected from 41 in-patients with a diagnosis of Acute and Transient Psychotic Disorder. Holmes and Rahe Stress Scale for stress in the preceding year, and Brief Psychiatric Rating Scale at baseline and follow up (4–12 weeks) for psychopathology were applied. IL-6, TNF-α (pro-inflammatory), TGF-β (anti-inflammatory) and Cortisol (morning and afternoon values) were measured at baseline and follow up.

A total of 30 out of 41 cases recruited had follow up data available. The levels of IL-6 ($p < 0.001$), TNF-α ($p < 0.001$) and TGF-β ($p < 0.001$) at baseline were all found to be significantly elevated compared to 42 age and gender matched healthy controls. There was a significant increase in the levels of TNF-α ($p = 0.020$) and morning levels of cortisol ($p = 0.009$) and a significant decrease in the levels of TGF-β ($p = 0.004$) and afternoon levels of cortisol ($p = 0.043$) from baseline to follow up.

This study showed that there was an increased level of both pro and anti-inflammatory cytokines at baseline and a prolonged pro – inflammatory compared to anti – inflammatory response which warrants larger prospective studies and comparative studies to patients with schizophrenia and bipolar disorders.

1. Introduction

The existence of typical acute psychotic syndromes has been documented in the psychiatric literature across many cultures for over a century and a half (Malhotra, 2007). However, Acute and Transient Psychotic Disorders (ATPD) was formally introduced into the nosology only with the advent of the ICD – 10 (World Health Organization, 1993). Following this, a large number of studies have been conducted to ascertain its diagnostic validity. These have focussed largely on demographic factors, precipitating factors, diagnostic stability and course and outcome (Malhotra and Singh, 2015).

ATPD is seen more commonly in developing countries (Susser and Wanderling, 1994), in women than in men and in people from a poorer socio-economic background (Malhotra et al., 1998; Susser et al., 1995a, 1995b). In developing countries, ATPD has a relatively high diagnostic stability (54–73%) and low rates of relapse (Malhotra and Singh, 2015). It is known to be related to stress both biologically and in relation to socio-cultural factors as borne out by an increased number of negative life events, febrile illnesses and childbirth in these patients (Collins et al., 1999; Cooper et al., 1990; Malhotra et al., 1998)

The presence of stress is known to elicit a 'stress response' in the body which involves the immune and endocrine systems, and can

☆ No conflicts of interest. Financial support for the project was provided from the Institute Intramural fund for postgraduates, which is provided by JIPMER to students while doing their postgraduate thesis. No other acknowledgements.
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http://dx.doi.org/10.1016/j.ajp.2016.11.010
1876-2018/

have various effects including the precipitation of an acute episode of mental illness (Rabkin and Struening, 1976).

The vulnerability-stress model of psychosis posits that symptoms emerge whenever a threshold of stressors exceeds the individual's vulnerability level, which is noted to be a stable characteristic (Zubin et al., 1983).

The hypothalamic-pituitary-adrenal (HPA) Axis has been proposed as being one of the mediators of stress related immune changes in psychotic illnesses such as schizophrenia (Zhang et al., 2005). Findings of elevated baseline cortisol (Christie et al., 1986; Ryan et al., 2004) and a blunted cortisol awakening response (Mondelli et al., 2010) in patients with first episode psychosis have suggested the possibility of dysfunction in the HPA Axis.

There is also noted to be a bidirectional relationship between the neuro-endocrine and the immune systems which is facilitated by cytokines (Sternberg, 1999). Cytokines are produced in the periphery by a variety of immune cells. They may be classified based on their actions into pro-inflammatory or anti-inflammatory types or on their source of production into T helper 1 (Th-1) or T helper 2 (Th- 2) types.

Th-1 lymphocytes release cytokines that enhance the cell mediated immune response and are mainly pro-inflammatory (e.g. IFN-γ, IL-1, IL-6, TNF-α, IL-2) while Th-2 lymphocytes release cytokines (e.g. IL-4, IL-5, IL- 10, IL-13, TGF-β) that enhance the humoral response by activating cells to express antibodies and are mainly anti-inflammatory. Equilibrium between pro- and anti-inflammatory cytokines is essential to maintain homeostasis in the immune system (Vilcek, 2003). Perturbations in this balance have been implicated in the pathogenesis of physical and psychiatric illness.

Significantly increased levels of IL-6 (Dunjic-Kostic et al., 2013; Frommberger et al., 1997; Ganguli et al., 1994; Kaminska et al., 2001; Kim et al., 2000, 2009; Kubistova et al., 2012; Lin et al., 2011; Na and Kim, 2007; Naudin et al., 1996; Pae et al., 2006), tumor necrosis factor-α (TNF-α) (Kaminska et al., 2001; Kim et al., 2009; Kubistova et al., 2012; Na and Kim, 2007; O'Brien et al., 2008) and transforming growth factor-β (TGF-β) (Kim et al., 2004, 2009) are seen in acutely relapsed in-patients with schizophrenia (first episode and previously treated) compared to control subjects. The most replicated findings amongst all cytokines studied were for IL-6 followed by TNF-α (Miller et al., 2011). The effect of antipsychotic treatment on levels of cytokines is more inconsistent. Three studies showed decreases in levels of IL-6 post treatment which correlated with changes in symptomatology (Frommberger et al., 1997; Na and Kim, 2007; Pae et al., 2006). TNF-α levels were not significantly different post treatment, while TGF-β levels post treatment decreased in two studies (Kim et al., 2004, 2009).

Similar findings were also noted in medication naive patients with first episode psychosis who in the acute phase had increased levels of IL-6 and TNF-α as compared to healthy controls. Treatment effects in this group of patients was also noted to be inconsistent (Upthegrove et al., 2014).

There have been no studies of immune markers specifically in ATPD which are etiologically known to be linked to stress in a majority of cases.

Our study thus aimed to explore the association between physical and psychological stressors and imbalances in pro-inflammatory and anti-inflammatory cytokines, HPA axis activity, and their association with disease activity in ATPD.

We hypothesized that in patients with ATPD there would be elevated levels of pro- and anti inflammatory cytokines at baseline associated with a blunted cortisol response which would be correlated with stressful life events which would normalise with treatment and correlate with changes in psychiatric symptomatology.

2. Methods

2.1. Study population and methods

This study was a single centre prospective exploratory study where a total of 41 inpatients, between the age of 18 to 60 years with the diagnosis of Acute and Transient Psychotic Disorder admitted at the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India between March 2012 and June 2013 were included. All patients fulfilled the ICD – 10 DCR Criteria for Acute and Transient Psychotic Disorder at study intake. Patients with delirium, organic or substance induced psychotic disorders; fever, clinical evidence of active infection or wounds; with other previously diagnosed serious medical illnesses; already using steroids, oral contraceptives or other immune modulators for medical indications; who were pregnant or breast feeding and those already treated with antipsychotics for the current episode were excluded from the study.

As part of the study, 42 age and gender matched controls were recruited. They had no history of any psychiatric or chronic medical illness, recent febrile illness, any clinical evidence of active infection or intake of any immune-modulatory medications at the time of sample collection. The control group subjects were explained the details of the study following which informed consent was obtained.

A semi structured detailed work up proforma administered in a face-to-face interview was employed to record salient features from the history, general physical examination and mental status examination at baseline. The diagnosis was made using ICD – 10 DCR criteria and verified by a consultant psychiatrist. Following this patients were reassessed between 4 and 12 weeks from baseline. All patients were psychotropic drug-free for at least 3 months at intake into the study. No medications were withdrawn in any of the study patients for the purpose of the study. Informed consent was obtained from either the patient, or the guardian of the patient, if the patient was not in a fit state to provide consent, after a complete description of the study to the patients and the guardians in their own language. Approval for the study was obtained from the Institute Ethics sub-committee for human studies. The patients received treatment as usual with antipsychotic medication at adequate doses, benzodiazepines as needed, and any other medications, if required.

2.2. Measures employed

2.2.1. Brief psychiatric rating scale (18 item version) (Overall and Gorham, 1962)

Applied during baseline and follow up visits to assess the degree of psychopathology

2.2.2. Holmes and rahe stress scale (Holmes and Rahe, 1967)

Used to quantify the stressful events over the past one year in the patient's life.

These scales have been applied previously for studies in the Indian population (Rao et al., 1985; Singal et al., 2015; Venkatesan, 2010) and were chosen for the ease of administration and that they could be used even if the patient was uncooperative.

The scales were applied by the principal investigator of the study who was not blinded to the diagnosis.

2.3. Collection of blood samples and biochemical analysis

Blood samples for IL-6, TNF-α, TGF-β and cortisol were drawn from the antecubital vein at 8 AM, with an additional sample for cortisol being drawn at 1 PM to account for the diurnal variation in