



Research paper

Alteration of immune markers in a group of melancholic depressed patients and their response to electroconvulsive therapy



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ABSTRACT

Background: Immune system dysfunction is implicated in the pathophysiology of major depression, and is hypothesized to normalize with successful treatment. We aimed to investigate immune dysfunction in melancholic depression and its response to ECT.

Methods: 55 melancholic depressed patients and 26 controls participated. 33 patients (60%) were referred for ECT. Blood samples were taken at baseline, one hour after the first ECT session, and 48 h after ECT series completion.

Results: At baseline, melancholic depressed patients had significantly higher levels of the pro-inflammatory cytokine IL-6, and lower levels of the regulatory cytokine TGF- β than controls. A significant surge in IL-6 levels was observed one hour after the first ECT session, but neither IL-6 nor TGF- β levels normalized after completion of ECT series. Seventy per cent ($n=23$) of ECT recipients showed clinical response and 42% ($n=10$) reached remission. Neither IL-6 nor TGF- β changes correlated with clinical improvement following ECT. No significant changes in IL-10, TNF- α and CRP levels were found in relation to melancholia or response to ECT.

Limitations: As a naturalistic study, some potential confounders could not be eliminated or controlled, including medication use.

Conclusions: Melancholic depressed patients demonstrated a peripheral increase in IL-6 and reduction in TGF- β , which did not normalize despite clinical response to ECT. These findings may be consistent with emerging hypotheses of the role of inflammation in mediating neurotrophin expression. The implications of chronic inflammation in the melancholic depressed population for future medical health, particularly cardiovascular risk, are largely unknown and warrant further investigation.

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1. Introduction

1.1. The cytokine theory of depression

The cytokine theory of depression postulates that major depressive disorder (MDD) results from enhanced production of peripheral proinflammatory cytokines which, acting as neuromodulators, represent the key factor in the (central) mediation of the behavioral, neuroendocrine and neurochemical features of depression (Schiepers et al., 2005).

Significant empirical support exists for a link between inflammation and depression, including: sickness behaviour, a syndrome that mimics several symptoms of depression following infection (Dantzer and Kelley, 2007; Dantzer et al., 2008; Goshen et al., 2008); development of a selective serotonin re-uptake inhibitor (SSRI)-responsive depression following cytokine immunotherapy (Capuron et al., 2002, 2009); increased rates of depression in populations with inflammatory conditions (Gold and Irwin, 2009; Kurd et al., 2010; Lichtman et al., 2008; Uguz et al., 2009); the association of immune dysregulation with psychological stressors that often precede episodes of depression (Carroll et al., 2011; Cole et al., 2007; Danese et al., 2009; Miller and Cole, 2012); the interaction of cytokines with the pathophysiological processes of depression (Miller et al., 2009); and the observation

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that antidepressants can have immunomodulating properties (Guloksuz et al., 2014). The evidence that a significant subset of depressed persons demonstrate upregulation of inflammatory markers also supports the complex, and likely bidirectional, relationship between depression and inflammation (Howren et al., 2009).

The most consistently replicated findings are for interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and the acute phase protein C-reactive protein (CRP) (Dowlati et al., 2010; Howren et al., 2009; Raison et al., 2006). Studies have shown evidence for increased proinflammatory to anti-inflammatory ratios in depressed populations (Dhabhar et al., 2009; Song et al., 2007). Peripheral pro-inflammatory cytokines are known from animal models to affect glial cell function, neurotrophic systems, and result in decreased neurogenesis, via free radical and glucocorticoid production (Song and Wang, 2011). However, the emerging evidence base on the association between depression and inflammation is complicated by numerous contradictory and negative studies coupled with wide variability in the reported levels of inflammation (Glassman and Miller, 2007). These conflicting study findings may partly be accounted for by the heterogeneity of the patient populations fulfilling criteria for diagnosis of MDD. It has been noted that increased consistency and specificity may be achieved by differentiating between clinical subtypes of depression (Baune et al., 2012; Lamers et al., 2013).

1.2. Melancholic depression as a distinct subtype of major depressive disorder

In DSM-5, melancholic depression is a subtype characterized by profound anhedonia, a distinct quality of depressed mood, diurnal mood variation, insomnia with early morning wakening, excessive guilt, significant anorexia or weight loss, and psychomotor retardation or agitation (American Psychiatric Association (APA), 2013). The proposed concept of melancholia as a biologically distinct subtype is supported by studies showing that it is more frequently associated with higher plasma noradrenaline levels (Kelly and Cooper, 1997; 1998); hypercortisolemia, as reflected in non-suppression of the dexamethasone suppression test (Shorter and Fink, 2010; Taylor and Fink, 2006); characteristic disturbances of the sleep architecture in electroencephalogram profiles (Armitage, 2007); and psychomotor disturbance, as measured by the CORE scale (Parker and Hadzi-Pavlovic, 1996). Melancholia has historically been considered to be predictive of a positive response to electroconvulsive therapy (ECT) and recent studies support this hypothesis (Fink et al., 2007; Hickie et al., 1996; Parker et al., 2001; Rasmussen, 2011).

Although some subtypes of depression have been linked with elevated inflammation (e.g., O'Donovan et al., 2013; Lanquillon et al., 2000; Raison et al., 2013), the field of psychoneuroimmunology has thus far offered only a few studies into differences in immune function in melancholic versus non-melancholic depression. One study found that cytokine production was reduced in acutely depressed melancholic patients, and normalized after treatment; whereas no change in cytokine production was observed in non-melancholic patients (Rothermundt et al., 2001b). Another study demonstrated activation of the hypothalamic-pituitary-adrenal (HPA) axis in melancholic patients, with partial normalisation upon remission, but failed to demonstrate activation of the cytokine system. (Kaestner et al., 2005). A positive association between serum levels of IL-6 and brain-derived neurotrophic factor (BDNF) was recently found in depressed patients, with IL-6 being a robust predictor of BDNF only in the melancholic depressed subgroup (Patras et al., 2014).

1.3. Immunological effects of ECT

There is strong evidence that ECT is an effective treatment for severe depression (Kennedy et al., 2009; UK ECT Review Group, 2003). However, since ECT was first introduced into psychiatric clinical practice in 1938 (Shorter and Healy, 2007), no consensus has yet emerged regarding its mechanism of action. The prevailing hypothesis is that ECT causes an alteration in the post-synaptic response to central nervous system (CNS) neurotransmitters; while promising animal research shows ECT can enhance hippocampal neurogenesis (Madsen et al., 2000; Perera et al., 2007). Successful ECT treatment has been shown to correlate with normalisation of HPA axis dysregulation (Bolwig, 2011). However, the immunological effects of ECT have received only limited research attention to date in small study samples. A recent review notes that ECT induces a transient immune activation, while repeated ECT may down-regulate immune activation, but this evidence is based on small studies (Guloksuz et al., 2014).

The first study exploring the effect of ECT on plasma cytokines demonstrated a dramatic increase in IL-6 ten minutes after seizure induction (Kronfol et al., 1990). This was replicated by a later study, which also showed an acute increase in IL-1 β for up to 6 h after ECT (Lehtimäki et al., 2008). Other acute effects of ECT include an increase in NK cell activity (Albrecht et al., 1985), IL-6 activity (Kronfol et al., 1990), leucocytes, IL-6, IL-10, and TNF- α (Fluitman et al., 2011).

Immunological effects following a course of ECT include increased numbers of activated lymphocytes (Fischler et al., 1992), reductions in pro-inflammatory cytokines IL-5 and eotaxin-3 (Rotter et al., 2013); and reductions in TNF- α , levels of which were shown to decrease in severely depressed patients along with clinical improvement with ECT, to become comparable to healthy controls by the end of the study (Hestad et al., 2003). Acute decreases in the absolute number of total blood lymphocytes and T8⁺ and Leu11⁺ cell subsets one hour after a single ECT session have also been shown in ten MDD patients (Fischler et al., 1992). In a separate study of ten MDD patients, baseline low levels, hypofunctionality and poor immunoreactivity of leukocyte G proteins normalized with ECT, and this normalisation of G protein measures preceded, and thus predicted, clinical improvement (Avisar et al., 1998). The existing study findings, although limited, indicate that ECT can act as an immunomodulatory agent by altering levels of cytokines and other immune markers most likely in the CNS, which are measurable in peripheral plasma.

Animal studies of electroconvulsive stimuli have shown an increase in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in brains of rats, notably in hippocampal and frontal areas (Angelucci et al., 2002); although other researchers have not demonstrated an increase in serum BDNF following electroconvulsive series in rats (Kyeremanteng et al., 2012). Monocyte secretion of BDNF has been demonstrated to be enhanced by IL-6 and TNF- α (Schulte-Herbrüggen et al., 2005); and positive association between IL-6 and BDNF has been found in clinical patients (Patras et al., 2014). van Buel et al. (2015) in a recent review of the literature, note the bidirectional influence of immune system activation and neurotrophins; and postulate that the acute increases in cytokines following ECT (such as IL-6), stimulate neurotrophin release, thus leading to hippocampal neurogenesis and clinical response.

1.4. Study aims and hypotheses

The aim of our study was to investigate differences in inflammatory markers between patients with melancholic major depression and healthy controls, and further to investigate the effect of ECT on the cytokine profiles of melancholic patients. Levels of the proinflammatory cytokines IL-6 and TNF- α , the anti-inflammatory cytokine IL-10, the regulatory cytokine TGF- β , and

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