Journal of Affective Disorders 155 (2014) 28–34

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Pro-inflammatory cytokine associated with somatic and pain symptoms in depression

Ya-Mei Bai [a,b,*], Wen-Fei Chiou [c,d,e], Tung-Ping Su [a,b], Cheng-Ta Li [a,b], Mu-Hong Chen [a]

[a] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] National Research Institute of Chinese Medicine, Taipei, Taiwan
[d] Institute of Life Science, National Taitung University, Taitung, Taiwan
[e] Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form
23 September 2013
Accepted 10 October 2013
Available online 18 October 2013

Keywords:
Pro-inflammatory cytokines
Somatic and pain symptoms
Depression

ABSTRACT

Background: More than two-thirds of depressed patients complain of somatic and pain symptoms, which are frequently regarded as a psychological reaction. Although there is a growing body of evidence showing that depression is related to immune abnormalities, few studies have investigated the association between inflammatory cytokines and somatic/pain symptoms.

Method: Patients with depressive disorder but without any medical disorders, and age/gender/body mass index (BMI)-matched healthy subjects were enrolled. All the subjects completed the self-rating scales of the Beck Depression Inventory-II and the Depression and Somatic Symptoms Scale, which was comprised of depressive, somatic, and pain subscales. Pro-inflammatory cytokines, including C-reactive protein (CRP), interleukin-2 receptor (sIL-2R), soluble interleukin 6 receptor (sIL-6R), soluble TNF-receptors (sTNF-R), soluble P-selectin (sP-selectin), monocyte chemotactic protein-1 (MCP-1), and adiponectin, were assessed by enzyme-linked immunosorbent assays.

Results: In all, 109 patients with depressive disorder and 126 normal controls were enrolled. The patients with depressive disorder had significantly more severe depression, somatic and pain symptoms (all $p<0.001$), and higher levels of sIL-2R ($p<0.0001$), sTNF-R ($p<0.001$), and sP-selectin ($p=0.005$) than the normal control group. Using multivariate regression analysis with controlling of age, gender, BMI, and other pro-inflammatory cytokines, sIL-2R was the most significant predictor for depressive symptoms ($p<0.0001$); with further controlling of severity of depressive symptom, sP-selectin was the only predictor for somatic ($p=0.002$) and pain ($p=0.059$) symptoms.

Conclusion: The elevated sP-selectin associated with somatic symptoms in depression, may indicate early micro-vascular changes occur subtly, and provide neurobiological evidence for somatic and pain symptom in depression.

1. Introduction

Research evidence has shown that a higher number of physical symptoms are highly predictive for depression and functional impairment (Nakao and Yano, 2006). More than two-thirds of depressed patients in primary care, especially patients in non-Western countries (Waza et al., 1999; Kim et al., 2011), reported only physical symptoms as the primary reason for their visit (Simon et al., 1999). Increased numbers of somatic or pain symptoms are associated with a greater severity of depression and a poorer quality of life (Hung et al., 2006, 2008; Hsu et al., 2009; Demyttenaere et al., 2006). Furthermore, somatic and pain symptoms are more difficult to treat than emotional symptoms (Greco et al., 2004), as the residual symptoms may worsen the treatment response (Karp et al., 2005; Papakostas et al., 2004), hinder full remission from depression (Vieta et al., 2008), and increase the risk of relapse (Hung et al., 2010). Improvement in painful and somatic symptoms is correlated with improvement in depression (Denninger et al., 2006; McIntyre et al., 2006), and is associated with higher remission rates (Fava et al., 2004). There is a growing body of evidence about the bidirectional relationships between depression and inflammation (Howren et al., 2009). Most of the evidence comes from these observations: (1) patients with major depression show elevated peripheral inflammatory biomarkers, even in the absence of a medical illness; (2) inflammatory illnesses are associated with greater rates of depression; and (3) patients treated with cytokines are at a greater risk of developing depressive disorder, and administration of anti-cytokines to patients with concurrent depression and

* Corresponding author at: Taipei Veterans General Hospital, Department of Psychiatry, No. 201, Shih-Pai Road, Section 2, Taipei 11217, Taiwan. Tel./fax: +886 2 28344012.
E-mail address: ymbi@mail2000.com.tw (Y.-M. Bai).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.10.019

inflammatory disease has resulted in relief of depressive symptoms (Sperner-Unterweger et al., 2012; Jones and Thomsen, 2012; McNamara and Lotrich, 2012; Rethorst et al., 2012; Capuron and Miller, 2011; Krishnadas and Cavanagh, 2012). Inflammatory mediators may alter monoamine and glutamate neurotransmission, glucocorticoid receptor resistance and adult hippocampal neurogenesis (Zunszain et al., 2012). Increased expression of inflammatory mediators in depressed patients may lead to a poor response to antidepressant drug therapy (Krishnadas and Cavanagh, 2012), and affect brain signaling patterns, cognition and the production of a constellation of symptoms, termed 'sickness behavior' (Capuron et al., 2001; Su, 2009). Inflammation-associated mood deterioration is reflected in changes in subgenual anterior cingulate cortex (sACC) (a region implicated in the etiology of depression) activity and functional connectivity during evoked responses to emotional stimuli. Peripheral cytokines modulate this mood-dependent sACC connectivity, suggesting a common pathophysiological basis for major depressive disorder and sickness-associated mood change and depression (Harrison et al., 2009). The reported pro-inflammatory cytokines related to depression included C-reactive protein (CRP), interleukin-2 (IL-2) (Capuron et al., 2001), interleukin-6 (IL-6) (Musselman et al., 2001), tumor necrosis factor alpha (TNF-alpha) (Moorman et al., 2007), monocyte chemotactic protein-1 (MCP-1) (Suarez et al., 2003), and P-selectin (Aschbacher et al., 2008, 2009; Do et al., 2010; Morel-Kopp et al., 2009; Musselman et al., 1996), which is a marker for platelet activity. However, results are not always consistent, which may be due to symptom heterogeneity of depression and anxiety (Duivis et al., 2013). A meta-analytic review showed depression and CRP, IL-1, and IL-6 are positively associated with a dose–response relationship (Howren et al., 2009). However, another meta-analysis showed significantly higher concentrations of the TNF-alpha and IL-6 in depressed subjects compared with control subjects; but there were no significant differences for other cytokines, including IL-1beta, IL-4, IL-2, IL-8, IL-6,IL-10, and interferon (IFN)-gamma (Dowlati et al., 2010).

Although there is a great deal of evidence supporting the relationship between inflammatory reaction and depression, few studies have investigated the association between inflammatory cytokines and somatic/pain symptoms. Among 37 outpatients with major depression and 48 healthy controls, Euteneuer found increased pain sensitivity (by pressure pain thresholds test) in depression may be linked to increased TNF-alpha concentration (Euteneuer et al., 2011). Another Netherlands Study, among 2861 participants, including patients with depression and normal controls, they found depressive symptoms were associated with higher levels of CRP, IL-6 and TNF-alpha. This association was mainly driven by somatic symptoms, which were associated with higher levels of CRP, IL-6 and TNF-alpha (Duivis et al., 2013).This condition of limited studies may be partially due to the lack of an assessment of somatic symptoms on conventional scales. The 17-item HAMD scale contains only two items, or 11.5% of the total score, for somatic symptoms (Farabaugh et al., 2005). And only two of the 10 items on the MADRS scale address vegetative symptoms (decreased appetite and insomnia), and there are none for other somatic symptoms (Williams and Kobak, 2008). Depressed patients in non-Western countries are more likely to report somatic symptoms than patients in Western countries (Waza et al., 1999; Kim et al., 2011). The depression and somatic symptoms scale (DSSS) is a simple, self-administrated scale developed in Asia (Hung et al., 2006). The DSSS includes 12 items for depression (Depression Subscale), 10 items for somatic symptoms (Somatic Subscale), and 5 items for pain symptoms (Pain Subscale). The validity and reliability of the DSSS has been established (Hung et al., 2006), and the percentage of improvement in DSSS and HAMD scores after one month of pharmacotherapy are well correlated (Hung et al., 2006, 2006). The DSSS depression and somatic subscales are significantly correlated with the mental and physical subscales of the 36-item Short Form Health Survey (SF-36) (Hung et al., 2009). The somatic subscale is also highly correlated with the somatization subscale of the Symptom Checklist-90-Revised for patients with major depressive disorder (Hung et al., 2009). Therefore, the self-rated DSSS, with only 281 words in the Chinese version, is a convenient and valid assessment tool for both depression and somatic symptoms. In this study, we aimed to investigate the association between somatic/pain symptoms and pro-inflammatory cytokines among patients with depressive disorder and age/gender/body mass index (BMI)-matched healthy subjects. The study hypothesis was that the somatic and pain symptoms in depression are related to some inflammatory responses as a neurobiological pathology, and not only as a psychological reaction.

2. Methods and materials

The study subjects were patients that met DSM-IV criteria for major depressive disorder or minor depressive disorder; age, gender and BMI-matched normal controls were used as a comparison group. The exclusion criteria were co-morbidity with any physical illness (including any flu, allergic rhinitis, or dermatitis), and DSM-IV diagnosis of any of the following: lifetime history of schizophrenia, bipolar disorder or any other psychosis, mental retardation, organic mental disorder, or substance abuse in the past three months or dependence within the past six months; pregnant or breastfeeding. The age, gender and BMI-matched normal controls were interviewed by a psychiatrist using the mini-international neuropsychiatric interview (MINI) to exclude psychiatric illness. Medical history review, vital signs, and anthropometric measurements were taken to exclude medical illness. All subjects completed the self-rated scales of the Beck depression inventory-II (BDI-II) and the depression and somatic symptoms scale (DSSS). The DSSS is composed of 22 items with three major subscales: a depression subscale, somatic subscale and pain subscale. The depression subscale has 12 items, including three vegetative symptoms and fatigue; and the somatic subscale has 10 items, including five pain items, which comprised the 5-item pain subscale. Cronbach's alpha values of the DSSS and its subscales ranged from 0.73 to 0.94 (Hung et al., 2006, 2006, 2009).

The pro-inflammatory cytokines of all subjects, including CRP, soluble interleukin-2 receptor (sIL-2R), soluble interleukin 6 receptor (sIL-6R), soluble TNF-receptors (sTNF-R), soluble P-selectin (sP-selectin), MCP-1, and adiponectin, were assayed using enzyme-linked immunosobent assay (ELISA) kits (R&D systems, Minneapolis, MN, USA). The lower detection limit of CRP is 0.010 mg/L and the sensitivity is 0.005 ng/mL. Specificity: natural and recombinant human CRP. Cross-reactivity**:** $<0.5\%$ cross-reactivity observed with available related molecules. $<50\%$ cross-species reactivity observed with species tested. The lower detection limit of sIL-2R is less than 10 pg/mL. Specificity: natural and recombinant human IL-2 sR alpha Cross-reactivity: $<0.5\%$ cross-reactivity observed with available related molecules. Cross-species reactivity not tested. The lower detection limit of sIL-6R is 6.5 pg/mL and the sensitivity is 1.5 pg/mL. Specificity: natural and recombinant human IL-6 sR. Cross-reactivity: $<0.5\%$ cross-reactivity observed with available related molecules. Cross-species reactivity not tested. The lower detection limit of sTNF-R is 0.77 pg/mL, and the sensitivity is 0.43 pg/Ml. Specificity: natural and recombinant human sTNF-R Cross-reactivity: $<0.5\%$ cross-reactivity observed with available related molecules. $<50\%$ cross-species reactivity observed with species tested. The lower detection limit of sP-selectin is less than 0.5 ng/Ml. Specificity: natural and recombinant human sP-Selectin. Cross-reactivity: $<0.5\%$ cross-reactivity observed with available related molecules. Cross-species reactivity not tested. The lower detection limit of