International Journal of Psychophysiology 81 (2011) 191–197

Contents lists available at ScienceDirect

International Journal of Psychophysiology

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

Psychological distress, depressive symptoms, and cellular immunity among healthy individuals: A 1-year prospective study

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ARTICLE INFO

Article history:
Received 15 April 2011
Received in revised form 17 June 2011
Accepted 20 June 2011
Available online 6 July 2011

Keywords:
Psychological distress
Depressive symptoms
Immune system
Natural killer cells
Lymphocyte

ABSTRACT

Cross-sectional and case-control studies have reported that psychological distress and depression are associated with reduced cellular immune competence but the directionality of the relationship remains uncertain. This study investigated whether levels of psychological distress and depressive symptoms are related to subsequent changes in counts of lymphocyte subsets (natural killer (NK), B, and T cell) and/or whether changes of immune markers predict psychological distress/depressive symptoms in a 1-year prospective study design. A total of 105 healthy employees (67 men and 38 women), aged 23–59 (mean 40) years with an average of 15 years of education, underwent a blood draw for the measurement of circulating immune cells and completed the Japanese version of the 28-item General Health Questionnaire (GHQ-28) and the Center for Epidemiologic Studies Depression Scale (CES-D) in April 2002 (time 1) and 2003 (time 2). Hierarchical multiple linear regression analyses revealed that GHQ-28 and CES-D scores at time 1 were significantly ($p<.05$) and inversely associated with NK cells at time 2 controlling for potential confounders including time 1 NK cells ($\beta = -.221$ and $-.177$, respectively). In contrast, NK cells and NK cell cytotoxicity at time 1 did not predict GHQ-28 or CES-D score at time 2 controlling for GHQ-28/CES-D score at time 1. GHQ-28 and CES-D scores were not related to T or B cells at times 1 and 2. The present findings indicate that psychological distress and depressive symptoms may precede and predict suppression of NK cell immunity while NK cells did not lead to subsequent psychological distress and depressive symptoms, suggesting an absence of the bi-directional relationships.

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1. Introduction

According to the World Health Organization (WHO), depressive disorders were the third leading cause of burden of disease in 2004 but are projected to be placed first by the year 2030 (WHO, 2008). Depressive disorders are identified as an independent risk factor for all-cause mortality (Cuijpers and Smit, 2002) and major medical illnesses including cardiovascular diseases (CVD) (Nicholson et al., 2006) and cancer (Pinquart and Duberstein, 2010). Substantial evidence suggests that depressive disorders are likely to involve several pathophysiological pathways and considerable attention is now paid to the possible role of immunological dysregulation in the pathogenesis of depressive disorders (Irwin and Miller, 2007).

A number of cross-sectional/case-control studies have reported that psychological distress and depression are associated with reduced cellular immune competence (Bauer et al., 1995; Evans et al., 1992; Frank et al., 2002; Jung and Irwin, 1999; Park et al., 2006; Schleifer et al., 1989; Tsuboi et al., 2005). According to several meta-analytic reviews (Herbert and Cohen, 1993; Weisse, 1992; Zorrilla et al., 2001), depressive disorders are associated with decreased natural killer (NK) cells, impaired NK cell cytotoxicity (NKCC), poorer proliferative response of lymphocyte to mitogens, and elevated CD4/CD8 ratios. Although the conclusion of meta-analysis studies implies that depression suppresses cellular immune function, a large part of literatures included in the analyses were cross-sectional/case–control studies which preclude causal inference.

To date, there are only a limited amount of studies that investigated the association between psychological distress/depression and cellular immunity using longitudinal approach (Amati et al., 2010; Evans et al., 2002; Fortes et al., 2003; Irwin et al., 1992; Leserman et al., 1997; McGuire et al., 2002). For example, in an 18-month prospective study, community-dwelling older adults with chronic but mild depressive symptoms had lower response to T cell proliferation tests compared to non-depressed counterparts from baseline to follow-up (McGuire et al., 2002). Another study in an elderly population (aged 65+ years) found a decrease in the relative

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0167-8760/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpsycho.2011.06.009

proportion of activated CD4+ (CD4+DR+) and CD8+ (CD8+DR+) T cells but not NK, CD4+, or CD8+ T cells in depressed compared to non-depressed individuals over a period of four years (Fortes et al., 2003). A series of follow-up studies in human immunodeficiency virus-infected patients demonstrated that depressive symptoms were consistently associated with decline of NK cell immunity (Evans et al., 2002; Leserman et al., 1997). A study of healthy nurses revealed that those who exhibited increased psychological distress (as measured by a 12-item General Health Questionnaire (GHQ)) had decreased CD4+ T cells and increased CD8+ and CD8+CD57+ T cells compared to those who maintained lower psychological distress after 1-year follow-up (Amati et al., 2010).

As such, psychological distress/depressive symptoms seem to be associated with suppression of NK and T cell function over time, however, there is an important question that remained unanswered, that is, whether or not psychological distress/depressive symptoms and cellular immune function are bi-directionally related even after adjustment for baseline dependent variable and extensive potential confounders such as health behaviors, physical condition, work-related factors, and medications. This question seems important because it has been debated that depression and immunity may have bi-directional relationships (Bjerkeset et al., 2011; Gimeno et al., 2009; Howren et al., 2009; Matthews et al., 2010; Pike and Irwin, 2006; Steptoe et al., 2003; Stewart et al., 2009) and depression has been characterized as a disorder of both immune suppression (defined as reduced proliferative responses of immune cells and impaired innate and adaptive immunity) and immune activation (defined as the proliferation of immune cells and the increased production of proinflammatory cytokines) (Blume et al., 2011).

Considering the above findings, the current study was designed to investigate the association of psychological distress and depressive symptoms with cellular immune markers in a 1-year longitudinal study design. Our purpose was to clarify the following two specific questions: (1) do levels of psychological distress/depressive symptoms at baseline associated with subsequent cellular immune competency adjusted for baseline immune variables? (2) Do immunological variables at baseline related to subsequent psychological distress/depressive symptoms adjusted for baseline levels of psychological distress and depressive symptoms?

We measured circulating NK, B, and T cells as well as NKCC because these markers are known to reflect quantitative and qualitative aspects of cellular immunity, reported to be associated with psychosocial factors including depression, and are commonly used indicators in human psychoimmunologic studies (Herbert and Cohen, 1993; Segerstrom and Miller, 2004; Weisse, 1992; Zorrilla et al., 2001). With regard to functional roles of selected lymphocytes, T and B cells bear central roles in cellular and humoral immunity; subsets of T (CD4+ and CD8+) cells control production of immunoglobulins from B cells and secretion of cytokines. NK cells are large granular cells possessing killer activity against certain tumor cells and virus-infected cells without prior sensitization.

2. Methods

2.1. Study participants

The study was conducted as a part of annual occupational health examinations in April 2002 and 2003. All participants were full-time Japanese employees working in daytime with an average of 15 years of education. A total of 217 employees who underwent health examination were invited to participate in this study and the survey questionnaire including purpose, instruction, and informed consent was given to them in April, 2002 (Baseline, time 1). Overall, 216 employees agreed to participate in the questionnaire survey and blood test, and replied with a signed consent form. Of these employees, 47 were excluded because of missing data in essential study parameters. An additional 21 employees reporting physical/mental disorders were excluded (see 'Covariates' section for detail), which resulted in a sample size of 148 participants at time 1. In April 2003 (Year 1, time 2), we followed-up 121 participants at the annual health examination (follow-up rate 81.8%). Of these employees, 16 were excluded because of missing data or reporting physical/mental disorders. In consequence, 105 healthy participants (67 men and 38 women) who provided complete sets of measurements in times 1 and 2 were enrolled in the analyses. Employees who participated in both times 1 and 2 and those who participated only in time 1 (non-participants) were similar except that non-participants were three years older, consumed more alcohol beverages, and showed slightly lower GHQ-28 score.

The study protocol was reviewed and approved by the Institutional Review Board of the National Institute of Occupational Safety and Health, Japan and by the Ethical Committee of the Kyushu University.

2.2. Measurements

2.2.1. Psychological distress

Psychological distress was assessed using the Japanese version (Iwata and Saito, 1992) of the 28-item GHQ (GHQ-28) (Goldberg and Hillier, 1979). We used Likert scale from 1 to 4, to calculate the score. If there are five or fewer missing responses on the GHQ-28, the total GHQ-28 score was calculated based on the following formula: "GHQ-28 score" = "sum of item scores answered (X)" × "28/X." The internal consistency (Cronbach's α) of the GHQ-28 in the present sample (n = 105) was 0.90 at time 1 and 0.88 at time 2.

2.2.2. Depressive symptoms

Depressive symptoms were measured using the Japanese version (Shima et al., 1985) of the CES-D (Radloff, 1977). The 20-item depressive symptom scale measures the level of depressive symptoms experienced in the past week. If there are three or less missing responses on the CES-D, the total CES-D score was calculated based on the following formula: "CES-D score" = "sum of item scores answered (X)" × "20/X." The Cronbach's α of the CES-D scale was 0.82 at time 1 and 0.87 at time 2.

2.2.3. Preparation of blood samples

Fasting blood samples were collected between 9.00 and 11.00 a.m. from participants to control for diurnal variations. Immunological parameters were determined by standard techniques, as described in detail elsewhere (Nakata et al., 2000; Nakata et al., 2010; Nakata et al., 2002). We determined counts of total leukocytes and total lymphocytes by an automated cell counter (Coulter Counter SP-VI, Coulter Electronics, Hialeah, FL).

2.2.4. Cell surface marker analysis

The following sets of monoclonal antibodies were used to perform four-color direct immunofluorescence surface-marker analysis: anti-CD45-FITC/anti-CD56-RD1/anti-CD19-ECD/anti-CD3-PC5. Anti-CD45-FITC antibody was used to identify and differentiate lymphocytes from non-lymphocytes and debris. A combination of Mouse IgG1-FITC/Mouse IgG1-RD1/Mouse IgG1-ECD/Mouse IgG1-PC5 was used as the negative control. All monoclonal antibodies were purchased from Beckman Coulter Inc, USA. We calculated the number in each lymphocyte subset by multiplying lymphocyte counts by the percentage of positive cells in each category, as determined by flow cytometer (EPICS XL, Beckman Coulter Inc, CA).

2.2.5. Cytotoxicity assay

A standard 4-hour Chromium-51 (^{51}Cr) release assay was used to determine NKCC with effector cells at an effector/target [E/T] cell ratio