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SHORT COMMUNICATION

Day-to-day cause—effect relations between cellular immune activity, fatigue and mood in a patient with prior breast cancer and current cancer-related fatigue and depression

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Summary This study of a breast cancer patient with cancer-related fatigue (CaRF) and depression investigated the bidirectional cause-effect relations between cellular immune activity, fatigue and mood during 'life as it is lived'. The 49-year-old patient (breast cancer diagnosis 5 years earlier, severe CaRF and increase in depressiveness since then) collected her entire urine for 28 days in 12-h intervals (from 8 p.m. to 8 a.m. and from 8 a.m. to 8 p.m.; total: 55 measurements) for the determination of urinary neopterin (immune activation marker) and creatinine levels using HPLC. Furthermore, she completed questionnaires twice each day (at approx. 8 a.m. and 8 p.m.), which yielded information on mood (3-Skalen-Eigenschaftswörterliste [EWL]) and fatigue levels (visual analog scale [VAS]). Cross-correlational analyses showed complex connections between urinary neopterin concentrations and mood and fatigue in terms of direction of effect, temporal delay and response pattern. Increases in urinary neopterin levels significantly preceded increases in fatigue intensity with a temporal delay of 60—72 h (lag 5: $r = 0.298$; $p = 0.027$), whereas increases in positive mood co-occurred with neopterin level increases (lag 0: $r = +0.302$; $p = 0.025$) and preceded decreases in neopterin concentrations with a temporal delay of 132—144 h (lag 11: $r = -0.323$; $p = 0.017$). These results confirm and extend our previous findings and show that in order to obtain an adequate understanding of the dynamic relations among cancer-related variables, the characteristics of everyday-life conditions need to be considered.
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1. Introduction

Evidence from conventional data-averaging studies on the association between immune activation, cancer-related fatigue (CaRF) and depression is equivocal. Although meta-analyses of 18 studies revealed clear evidence of an overall positive association between CaRF and levels of interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra) and neopterin, the pooled correlation estimate on, for example, the association between CaRF and IL-6 levels showed substantially varying *r*s, ranging from 0.62 to −0.54 (Schubert et al., 2007). There are similar inconsistencies in the literature regarding the relation between depression and immune activity in cancer (Reiche et al., 2004). For instance, while a study on breast cancer patients showed that a four-month psychological group intervention reduced inflammatory markers by alleviating depressive symptoms (Thornton et al., 2009), a more recent study suggests that decreased depressive mood is associated with generally increased inflammatory reaction in cancer (Kim et al., 2012).

To date, studies of the relation between immune activation, CaRF and depression are limited in that they do not consider how immune parameters, fatigue and mood interact in real life, i.e. under conditions where they can dynamically unfold without too many spatial and temporal restrictions (Schubert et al., 2009). The temporal delays between mood, fatigue and immune activity are not known, and the direction of effects and response patterns have not yet been sufficiently investigated during ''life as it is lived'' (Allport, 1942). A failure to consider dynamic features in psychosomatic research can result in inconsistent findings and may hinder development of effective treatment strategies, which should be based on an understanding of the functional characteristics of biopsychosocial phenomena under everyday-life conditions (Schubert et al., 2012).

We deal with these methodological problems of nomothetic research by applying an alternative idiographic approach (''integrative single-case studies'') that investigates individuals intensively over time and generalizes findings through replication (Barlow and Nock, 2009). Using this approach, we recently provided first evidence of real-life cause-effect relations between fatigue, mood and urinary neopterin levels in a 60-year old breast cancer patient. For that patient, who did not suffer from CaRF or depression, time series analysis of 31 consecutive daily measurements revealed that increases in urinary neopterin levels significantly preceded increases in fatigue after 24 h. Moreover, decreases in mood preceded increases in urinary neopterin levels after 96 h (Schubert et al., 2009). Neopterin was used for immunological analysis because it is a good marker of cellular immune activation and has been associated reliably with CaRF and depression (Fuchs et al., 1992; Schubert et al., 2007). A limitation of that study, however, was that only daytime data (over 31 days) were available, thus hampering proper time series analysis (Schubert et al., 2009).

The present study differed from the above-mentioned study in several important aspects, and it provided a more valid representation of the topic under investigation. For one, the breast cancer patient of the current study suffered from CaRF and depression. Moreover, the study design was improved considerably by including daytime and nighttime data. Over a period of 28 days, this resulted in almost doubled measurements (55 vs. 31) and gapless time series. Having more than 50 measurements in 12-h intervals allowed us to control for serial dependencies, through autoregressive integrated moving average (ARIMA) modeling (Box and Jenkins, 1976), and to identify complex patterns of association between immune activity, mood and fatigue.

2. Methods

2.1. Study design

This study is part of a larger project on breast cancer survivors that is investigating the influence of emotionally meaningful incidents on stress system dynamics. Prior to the study start, the patient received thorough medical and psychological examination to ensure that she met all inclusion and exclusion criteria specified by Bower et al. (2002). The only difference to the latter was that our patient had been diagnosed with dysthymia (F34.1) and adjustment disorder (F43.21).

The patient collected her entire urine for 28 days (from July 13th to August 9th, 2006) in 12-h intervals (from approx. 8 p.m. to 8 a.m. and from approx. 8 a.m. to 8 p.m.) to determine urinary neopterin levels (total: 55 measurements). Furthermore, she answered questionnaires retrospectively every 12 h, i.e. at approx. 8 a.m. and 8 p.m. Once a week, the patient brought the frozen (−20 °C) urine sample aliquots to the laboratory, where they were stored at −70 °C until analysis. At these regular weekly appointments, she was also interviewed and medically evaluated.

The patient gave written informed consent, and the Ethics Review Committee of Freiburg University approved the design.

2.2. Description of the patient

The patient is a married, college-educated 49-year-old Caucasian woman with three children. She is a non-smoker and consumes alcoholic beverages on a moderate basis. She has no history of immunological or endocrinological disease or diseases that could affect immune and endocrine function except those at the focus of this study. 5 years before study start, the patient was diagnosed with a ductal mamma carcinoma (C50.4) in her right breast (pT2, pN1biv (6 of 13), cM0, G3, R0, ER 10%, PR 70–80%, HER2+/neu+, score = 3). Primary cancer therapy consisted of surgery, radiotherapy and anti-estrogen therapy. Adjuvant therapy with tamoxifen (anti-estrogen) ended 6 months before the start of the study. Both before and since her cancer diagnosis, the patient has suffered from dysthymia (F34.1).

Shortly after cancer diagnosis and therapy, the patient developed severe chronic fatigue (CaRF) and a substantial increase in depression intensity with clear functional impairment (clinical diagnosis: adjustment disorder with depressed mood, F43.21), both lasting until study start. The long duration of depressive symptoms may have been due to the underlying dysthymia and adjustment problems triggered by repeated follow-up cancer checks. The patient had seen a psychotherapist for 6 months, ending 5 months before study start.

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