The sequelae of chronic stress: Immunity and health

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Abstract

To examine the interactions among social support, chronic stress, immune function, and infectious illness in older adults, we assessed changes in immune function and health in 69 spouses who had been providing care for a husband or wife with Alzheimer’s disease for an average of 5 years and 69 sociodemographically-matched control subjects. Data were collected at two points in time, the initial sample (“intake”) and follow-up, an average of 13 months later. We also assessed social support and depression. Depression was assessed using the Structured Clinical Interview for DSM-III-R and the Hamilton Depression Rating Scale. Immunological assays included three functional assays, blastogenesis using concanavalin and phytohemagglutinin, and antibody titers to Epstein-Barr virus as a measure of the effectiveness of the cellular immune response to control latent virus.

Caregivers showed decrements relative to control subjects on all three measures of cellular immunity. Caregivers also reported significantly more days of infectious illness, primarily upper respiratory tract infections. Caregivers had a much greater incidence of depressive disorders than controls, with 25% of follow-up, compared to no cases among controls at intake and 6% at follow-up. Caregivers who reported lower levels of social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up.

These findings may be particularly important for older adults, since immune function declines with age. For individuals who are more chronically stressed, there could be longer-term, potentially important consequences for health.

Introduction

Considerable evidence has suggested an association between the occurrence of short-term stressful events and downregulation of immune function. In particular, studies from our laboratory showed decrements in a variety of immune function in blood samples drawn during an examination series, in contrast to lower stress “baseline” samples drawn about 1 month previously when students were not taking examinations [1–3]. The range of immune functions that appear to be affected by
the mild stressor has included natural killer (NK) cell activity, blastogenesis, antibody to several herpesviruses including Epstein-Barr virus (EBV), herpes simplex virus, type 1 (HSV-1), cytomegalovirus (CMV), specific T-cell killing of EBV-infected B-lymphocytes, and the levels of mRNA to the interleukin-2 (IL-2) receptor. Most recently, we found that the antibody response to the recombiant hepatitis B vaccine and the subsequent T-cell response to the vaccine are also altered by stress in medical students (see chapter by Glaser and Kiecolt-Glaser, this volume).

While these are provocative data showing short-term changes, the influence of very chronic or long-term stress on immune function has not been studied as closely. Data from rodent studies have suggested that an acute stressor may be associated with immunological downregulation, and that chronic stress may be associated with adaptation, or even immunological enhancement [4]. In the studies described in this paper, we addressed the effects of a chronic stressor that covered several years or more and its association with alterations in immune function, using older adults who were providing care for an Alzheimer’s disease (AD) victim [5–7].

In our assessments of the mental health of this population, we found that among AD spouses who have been providing care for an average of 5 years, 30% of these spouses met diagnostic criteria for syndromal depressive disorders. Similarly, among adult children who are providing care for a parent, 24% have met criteria for depressive disorder, and 10% for an anxiety disorder during caregiving [6]. These rates are considerably higher than the 1–5% found among well-matched control subjects.

While caregiving for a demented relative is clearly an extraordinarily long-term, unpredictable, and uncontrollable stressor, caregivers show a wide variability in their responses [8]. Social support is one of the variables that has been most strongly associated with differences in caregivers’ mental health, we felt it might also be a variable in the modulation of immune function; research with diverse populations has shown an association between cellular immune function and the quality of personal relationships, providing one possible physiological pathway between personal relationships and health [9].

Methods

The methods for this larger study are described in more detail elsewhere [5–7]. Spousal caregivers for AD victims who had been providing at least 5 h or more of care per week were recruited for this study. The average subject had been providing care for 5.2 years (SEM = 0.55) at intake, and reported spending an average of 8.26 h/day caregiving (SEM = 0.68) at intake, and 7.74 (SEM = 0.60) at follow-up. The mean time between intake and follow-up sample points was 13 months. Subjects were interviewed extensively, including the Structured Clinical Interview for DSM-III-R (SCID-R), the Hamilton Depression Rating Scale, the Social Support Interview, and the Memory and Behavior Problem Checklist (MBPC) [10–13]. Health-related behaviors, assessed at each interview, included medication use, caffeine intake, and alcohol intake. Subjects described current sleep status and any recent changes in sleep and weight. To assess infectious illness episodes, we used the Health Review [14], as described elsewhere [7], and found excellent concordance between the health review and physicians’ assessment of illness. Immunological assays included blastogenesis with two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA), as well antibody titers to EBV virus capsid antigen (VCA) IgG.

Results

Caregivers were significantly more depressed than control subjects, both in the frequency of syndromal depression and in the severity of depressive symptoms as measured by the HDRS. Moreover, the social support interview showed that caregivers had fewer people in their networks, rated the networks as less helpful, and described contacts as less frequent and less close [7]. In addition, caregivers had significantly more days ill (primarily upper respiratory tract infections) and visited physicians more often than control subjects.

There were significant differences between controls and caregivers on all three of the functional immunological assays that were included in the study. The most dramatic changes occurred in antibody titers to EBV VCA where caregivers mean values more than doubled between the first and the second sample point. In order to assess the uniformity of change between caregivers and controls in this assay, we assessed the number of subjects within each group who showed an increase, a decrease or did not change from intake to follow-up; 77% of the caregivers had higher EBV VCA titers at follow-up compared to intake, while 35% of controls had higher titers and 40% had lower titers. Moreover, when we assessed data for Con A and PHA induced blastogenesis, we found a significant group by time interaction for both, with the greatest effects at the highest concentrations of mitogen. Thus, across three different functional assays, caregivers fared more poorly than control subjects. When we combined the data from these three immunological assays (by transforming differences between baseline to follow-up using z-scores), we assessed psychosocial factors associated with change in a hierarchical regression. After controlling for intake levels of EBV VCA, Con A, and PHA in the first step, we found in subsequent steps that caregivers showed reliably more change than controls; age and income were unrelated to change. However, and perhaps most interesting, lower social support at intake was significantly and reliably associated with greater negative immunological change at follow-up; moreover, the social support by group interaction showed that social support was most important for caregivers, compared to controls. We also examined the pattern of decline across all three functional assays, since such a pattern would suggest that individuals might be at particular risk. We found that 14% of controls and 32% of caregivers showed negative change across all three functional
assays. When we compared the one-third of the caregivers who showed decrements across assays (referred to as the "at-risk" caregivers) with the other two-thirds of the caregiver sample, we found no differences on age, education, income, health-related behaviors, or depression. However, there were significant differences in social support, with the at-risk caregivers who showed the most uniform declines reporting poorer social support, as well as a stronger and more negative response to dementia behaviors and a trend to greater illness [7].

Discussion

The study suggested that there could be longitudinal changes in certain aspects of immune function, health, and depression in spousal caregivers who are already quite distressed, and who had been providing care for a number of years [5,7]. These changes were contrasted to similar data obtained from well-matched control subjects. Neither the severity of depressive symptoms nor the presence of syndromal depression was reliably related to either intake levels or subsequent changes in immune function. As in other studies, the association between social support and immune function did not appear to be mediated via depression. The data provide no evidence of physiological adaptation over time.

These results may be most important for older adults, for whom there are already age-related declines in immune function [15–19]. For such individuals, stress could have significant and important consequences for health.

References