Stress Effects on Family Caregivers of Alzheimer's Patients

Research and Interventions

Enid Light, PhD
George Niederehe, PhD
Barry D. Lebowitz, PhD
Editors

1994

Springer Publishing Company
New York
that the chronic stresses of providing care for a family member who has Alzheimer's disease (AD) or another progressive dementia may be associated with chronic (and perhaps progressive) immunological changes. In addition, data suggest that caregiving is associated with more severe infectious disease episodes, primarily upper respiratory tract infections, consistent with our prior speculation that distress-related immunosuppression may have its most important health consequences in groups with other, pre-existing immunological impairments, such as older adults with age-related decrements in immune function (Kiecolt-Glaser & Glaser, 1991).

LONGITUDINAL CHANGES IN IMMUNITY AND HEALTH IN SPOUSES

In an earlier small cross-sectional study, we obtained psychological data and blood samples for immunological and nutritional analyses from 34 family caregivers of Alzheimer's Disease victims and 34 sociodemographically-matched comparison subjects (Kiecolt-Glaser, Glaser, Dyer, et al., 1987). In most caregiver studies (Light & Lebowitz, 1989), our caregivers were more distressed than comparison subjects without similar responsibilities. In addition, caregivers had poorer immune function than comparison subjects. However, these cross-sectional data did not provide data to assess the possibility of progressive immunological changes over time as suggested by the glucocorticoid cascade hypothesis (Sapolsky, Krey, & McEwen, 1986), or the relationship of any immunological changes to psychosocial variables such as personal relationships.

To better understand changes in caregivers over time, we followed the 86 spouses and 86 matched controls for whom baseline depression data were described above (Dura, Stuckenberg, & Kiecolt-Glaser, 1990). Of the original 86 spouses, 13 were no longer caregiving at follow-up due to their spouse's death, 2 subjects moved, 1 died, and 1 was unreachable. New matches were made where necessary among the 81 controls available at follow-up, leaving 20 men and 49 women in each of the two groups; the average age was 67 in both groups (Kiecolt-Glaser, Dura, Speicher, Trask & Glaser, 1991).

The average spousal caregiver had been providing care for about 5 years, and he/she provided around 8 hours of care on the average day. The modal subject reported an annual family income between $20,000 and $30,000. The majority of subjects were caucasian, 95% of caregivers and 93% of controls. Most noncaregivers were married (69%); however,
19% were widowed, 12% were divorced, and one comparison subject had never married. While we did not match our groups on marital status, the inclusion of divorced and widowed control subjects actually worked against confirmation of the experimental hypotheses, since intact marriages are associated with lower rates of psychopathology and less dysphoria (House et al., 1988).

**Health-Related Behaviors and Infectious Illness**

Health-related behaviors did not distinguish between caregivers and controls. There were no reliable group differences in alcohol consumption, medication use, caffeine intake, or plasma levels of albumin, a biochemical nutritional marker. While caregivers reported around two hours less sleep than controls in the preceding three nights, correlations between sleep and immunological data were small and unreliable.

To assess infectious illness episodes, we used the Health Review (Jenkins, Kraeger, Rose, & Hurst, 1980), a checklist of specific illness symptoms related to infectious diseases (primarily upper respiratory illness). All subjects were called every three months, read the symptom list, and asked to indicate which symptoms occurred as part of an illness episode, as isolated symptoms, or as more chronic problems, with operational definitions provided for these categories. Subjects were also asked whether they saw a physician for the problem(s), and how many days they reduced their activity because of each health change. The Health Review was validated against physician diagnoses in a study of air traffic controllers (Jenkins et al., 1980); as previously shown in that study, we obtained excellent agreement when we compared our assessments with physician data (Kiecolt-Glaser et al., 1991).

Caregivers experienced significantly more days illness from infectious disease, primarily upper respiratory tract infections, and they visited physicians significantly more often. Although caregivers and controls did not differ in number of illness episodes, there was evidence that caregivers had less frequent exposure to pathogens. In contrast to controls, caregivers had fewer people in their social support networks, they saw network members less frequently, and they received less helpful emotional and tangible support. Perhaps most importantly, caregivers spent an average of eight hours a day in caregiving activities.

**Changes in Immune Function Over Time**

We included assays to assess both quantitative and functional changes in cellular immunity. Functional assays included blastogenesis with two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA), as well as antibody titers to a latent herpes virus, Epstein-Barr virus (EBV). The latter assay was included because the cellular immune response is important in controlling latent herpes viruses (Glaser & Gotlieb-Stematsky, 1982). Psychological stress has adverse effects on cellular immunity, and there is evidence that this interaction can modulate latent herpes viruses (Glaser et al., 1987). With compromised cellular immunity, reactivation of latent herpes viruses can occur, and there are characteristic elevations in herpes virus antibody titers reflecting the antibody response to increased synthesis of the virus or viral proteins (Glaser et al., 1987; Glaser, Strain, Tarr, Holliday, Donnerberg, & Kiecolt-Glaser, 1985).

We found significant group differences on all three of the functional assays. The most dramatic changes occurred in caregivers’ antibody titers to EBV; while there were no differences between caregivers and controls at baseline, caregivers’ EBV antibody titers had almost tripled at follow-up.

In order to assess the uniformity with which caregivers and controls were changing on this measure, we examined the number of subjects within each group who showed an increase, decrease, or remained the same from baseline to follow-up. Fully 77% of caregivers had higher EBV virus capsid antigen (VCA) antibody titers in the follow-up sample compared to baseline, while 35% of controls had higher titers and 40% had lower titers. Thus, changes in caregivers did not simply reflect changes in only a few outliers.

Data for Con A and PHA showed significantly higher blastogenic values in controls than in caregivers. In addition, caregivers decreased relative to controls, and these changes were greatest at the highest mitogen concentrations. The differences related to mitogen concentration were particularly interesting because they suggested that the T-lymphocytes of caregivers responded much more like those of controls at lower concentrations, but increasing stimulation produced greater impairments in caregivers.

There was not a significant difference between caregivers and controls on the quantitative immunological measures (percent total T-lymphocytes, helper cells, and suppressor cells), nor was there an interaction between group and change from baseline to follow-up. Similarly, there were not significant changes in percentages of two other cell populations, natural killer (NK) cells and B-lymphocytes. Although functional aspects of cellular immunity have been implicated in age-related immunological declines that are thought to be associated with the risk and severity of infectious disease and the increased risk for malignant disease, most studies show no significant age-related changes in the percentages
of lymphocyte subpopulations (Inkeles, Ines, Kuntz, Kadish, & Weksler, 1977).

We were interested in examining characteristics of individuals who showed either consistent negative immunological changes across the functional measures, as well as those who showed the greatest changes overall. The first pattern, uniformity of immunological down-regulation, would suggest that these individuals were at particular risk, showing a consistent decline across measures. A total of 14% of controls and 32% of caregivers met this criterion, a clear and significant difference in risk between groups.

Among caregivers, we assessed differences between the one-third who met the criterion ("at-risk") and the two-thirds who did not. Surprisingly, there were no differences on age, education, income, health-related behaviors, or depression. However, there were interactions between group and change from baseline to follow-up on three dimensions of interest: social support, response to dementia behaviors, and health.

At-risk caregivers had lower social support at baseline than the other two-thirds of caregivers, with the two groups converging at follow-up; these data are consistent with the regression analyses discussed below. There was a trend (p < .08) for greater illness in the at-risk caregivers, particularly at follow-up. Finally, although at-risk caregivers did not differ from the remainder of the cohort in years of caregiving, hours per day, or severity of dementia, they did differ in their response to dementia-related behaviors as measured by the Memory and Behavior Problem Checklist scales (Dura, Bornstein, & Kiecolt-Glaser, 1990; Zarit, Orr, & Zarit, 1985). At-risk caregivers reported more distress, and more problematic behaviors.

Regression analyses were used to evaluate the contribution of social support to immune function. We constructed a summary immunological change measure by calculating percent change from baseline for each of the three functional assays (Con A, PHA, and EBV antibody titers), then normalized each of the three distributions by converting them to z-scores, and added the three z-scores together; higher values indicated greater negative change from baseline. Using a hierarchical regression model to predict change in immune function, baseline immune function was entered first, followed by group membership on the second step. Age and income were entered on the third step, to control for sociodemographic influences. Both the baseline and follow-up scores for helpful support (both tangible and emotional support) were entered on the next step. The group by baseline support interaction was entered on the fifth and final step. Baseline immune function was (as expected) a

strong and significant predictor of subsequent changes. In addition, as expected from the earlier analyses, caregivers fared more poorly in terms of change from baseline compared to controls. Neither age nor income made a significant contribution.

However, after controlling for baseline immune function, age, income, and group, both baseline social support and the group by support interaction were both significantly related to changes in immune function. Lower support at baseline was associated with greater downward changes in immune function, and these effects were more pronounced for caregivers than for controls.

We used an identical equation with baseline Hamilton depression scores (Hamilton, 1967) entered along with age and income on the third step to assess the possibility that the contributions of social support to changes in immune function simply reflected prior differences in depression. However, depression did not make even a marginal contribution to the variance, and the contributions of baseline social support and the interaction between group and support were unchanged after controlling for depression. As in Baron, Cutrona, Hicklin, Russell, and Lubaroff (1990), the association between social support and immune function was not mediated by depression.

We analyzed the data in several other ways to assess possible contributions of depression to group differences in immune function, since caregivers had higher levels of depressive symptoms than controls, as well as a much greater incidence of syndromal depressive disorders; 25% of caregivers met DSM-III-R criteria for a current episode at baseline, compared to no cases among controls. Similarly, 32% of caregivers met syndromal criteria at follow-up, compared to 6% of controls.

A number of studies have linked depression with impaired immune function (Schleifer, Keller, Heyerson, Raskin, Davis, & Stein, 1984; Schleifer, Keller, Siris, Davis, & Stein, 1985). High levels of depression are even associated with impairments at the molecular level, in the rate of the repair of cellular DNA repair (Kiecolt-Glaser, Stephens, Lipitz, Speicher, & Glaser, 1985). The degree of distress-related immunological impairment may be related to both the severity of depression and to age (Schleifer et al., 1985). However, among our spousal caregivers, neither severity of depressive symptoms nor presence of syndromal depression was even marginally related to either baseline levels or subsequent changes in immune function. Speculatively, the very long-term heightened distress and dysphoria shown by many caregivers may overshadow the contributions of clinical depression to immune function. Alternatively, the effects may not be as reliably mediated through depressive affect as through anxiety or more global dysphoria.
IMPLICATIONS OF SPOUSAL DATA FOR STRESS IN OLDER ADULTS

The longitudinal data from our laboratory showed decrements in functional aspects of immunity in caregivers compared to well-matched control subjects. These findings were particularly noteworthy because the average caregiver had already been providing care for five years at baseline, and thus might have been expected to show physiological adaptation. Caregivers also experienced longer infectious illness episodes and visited physicians more often. The caregivers who showed the greatest and the most uniform immunological declines were those who reported lower levels of social support at baseline and who were most distressed by dementia-related behaviors.

These findings may have particular importance for older adults. One of the hypothesized consequences of the glucocorticoid cascade hypothesis (Sapolsky et al., 1986) discussed earlier is the acceleration of the process of immunosuppression associated with aging. In spousal caregivers, who are older, chronic stress could have longer-term, potentially irreversible consequences.

The significant immunological decrements that accompany aging (Murasko, Weiner, & Kaye, 1988) are thought to be associated with the increased morbidity and mortality accompanying infectious disease in the elderly. Among adults over 75 years of age, pneumonia, and influenza together are the fourth leading cause of death (Yoshikawa, 1983). Acceleration of age-related declines in immune function could exacerbate risk and severity of infectious illness.

Immunological changes may also reflect changes in other systems. Evaluation of the blastogenic response in 403 older adults with a mean age of 86 showed that the lymphocytes of 18% did not proliferate in response to three mitogens (Murasko et al., 1988). While the overall mortality of the population for a 2-year period was 15%, negative responders had twice the mortality of positive responders. The major cause of death in both groups was sudden death or a diagnosable cardiovascular-related disease. The authors suggest that decrements in cellular immunity may reflect changes in other systems as well, and may provide one marker of physiological aging.

Similarly, a 16-year longitudinal study of 105 healthy elderly men showed that declines in the absolute number of peripheral blood lymphocytes were associated with subsequent mortality within three years of death when compared with 5 or 10 years before death (Bender, Nagel, Adler, & Andres, 1986). There was not an association between the decrease in numbers of lymphocytes and age at death, smoking status, or prior cardiac illness. Moreover, a 20-year longitudinal study of 273 healthy adults over 60 showed that poorer cell-mediated immunity was associated with subsequent morbidity and mortality (Wayne, Rhyne, Garry, & Goodwin, 1990).

CLINICAL IMPLICATIONS AND DIRECTIONS FOR FUTURE RESEARCH

There are clearly multiple adverse changes associated with dementia caregiving. Unfortunately, there are neither truly prospective data available to evaluate the full impact of caregiving, nor are there random samples of caregivers (Schulz et al., in press). In an attempt to assess the extent to which caregivers in our study differed from those who declined participation, we compared information available on respite care uses who elected to participate in our caregiving research project with similar information from individuals who declined the opportunity; nonparticipants provided care for more impaired patients. We also compared data from caregivers who were able to travel to our university clinic setting for evaluation with data from individuals we evaluated in their homes because they were unwilling or unable to leave their demented relative at home, despite the availability of free taxi service paid by the project; caregivers seen at home were significantly more depressed than those who came to the university. Putting these data together, caregivers who do not participate in caregiving research are likely to be more impaired (Dura & Kiecolt-Glaser, 1990); therefore, the available caregiver data may actually underestimate the scope of the problem to a significant extent. Moreover, the association between social support and immune function would also suggest that isolated caregivers who have more impaired patients may be one of the most important groups to target for respite care or other interventions.

Much remains to be done to understand the physiological impact of caregiving stressors. Pomara, Depta, Gallow, LeWitt and Stanley (1989) recently reported that spousal AD caregivers had significantly higher cerebral spinal fluid GABA concentrations than controls. The authors note that there is considerable literature suggesting a role for GABAergic systems in anxiety, with acute stressors in animals associated with alterations in GABA concentrations and in the activity of the GABA receptor-gated chloride channel in the brain. Clearly, there is growing evidence from multiple laboratories showing physiological alterations related to caregiving.

AD caregiving is a significant and important problem, with recent
studies (Evans et al., 1989) showing a far greater AD prevalence than previously suspected. While the data from caregiving studies are critical for understanding the impact on the caregivers themselves, they also have broader implications for aging research as well; through data collected on caregivers, we can obtain vital information about the interactions among immunity, stress, and aging, and the implications of these interactions for health.

**REFERENCES**


**NOTE**

While we found no differences between caregivers and controls in our previous study (Kiecolt-Glaser et al., 1988), we had followed Fiore et al. (1983) in using support averages rather than totals. Although there were not reliable differences between caregivers and controls when we assessed differences using averages, caregivers named significantly fewer people than controls, and thus totals were significantly different across the categories of frequency, closeness, helpful emotional support, and tangible emotional support. We elected to use totals because they appear to better represent the experience of caregivers.