

Chronic Stress Modulates the Immune Response to a Pneumococcal Pneumonia Vaccine

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Objective: Influenza and pneumonia account for significant morbidity and mortality, particularly in older individuals. Previous studies have shown that spousal caregivers of patients with dementia have poorer antibody and virus specific T cell responses to an influenza virus vaccine relative to noncaregiving control subjects. This study tested the hypothesis that stress can also significantly inhibit the IgG antibody response to a pneumococcal bacterial vaccine. **Method:** We measured antibody titers of current caregivers, former caregivers, and control subjects after vaccination with a pneumococcal bacterial vaccine. **Results:** Caregivers showed deficits relative to controls and former caregivers in their antibody responses to vaccination. Although the groups did not differ before vaccination or in the rise in antibody 2 weeks or 1 month after vaccination, current caregivers had lower antibody titers 3 and 6 months after vaccination than either former caregivers or controls. **Conclusions:** These data, the first evidence that chronic stress can inhibit the stability of the IgG antibody response to a bacterial vaccine for pneumonia, provide additional evidence of health risks associated with dementia caregiving. **Key words:** stress, immune response, vaccinations.

PSS = Perceived Stress Scale; ISEL = Interpersonal Support Evaluation List.

INTRODUCTION

A recent large population-based study of the elderly revealed that caregiving for an impaired spouse is a risk factor for mortality (1). Certainly, dementia caregiving can be quite taxing; family members must cope with severe behavioral problems including incontinence, the inability to communicate or recognize familiar people, and wandering. How does this long-term psychological stressor increase the risk for death?

A growing body of evidence has demonstrated that caregiving can downregulate or dysregulate many aspects of the immune response (2–6). These immune changes can have health consequences; for example, dementia caregivers exhibited significant deficits relative to

well-matched noncaregivers in both the antibody and virus specific T cell responses to an influenza virus vaccine (7). Additional work confirmed caregivers' poorer antibody responses to influenza virus vaccinations and also showed alterations in cortisol, a stress-responsive hormone (3). These data suggest that caregivers are potentially more vulnerable than their aged-matched peers to influenza virus infections, as well as other infectious agents (8).

Importantly, preliminary data suggest that cessation of caregiving does not necessarily terminate risk; in data from our longitudinal study, former spousal caregivers have not differed significantly from continuous caregivers on cellular immune function after the death of the impaired spouse. In fact, spousal caregivers have continued to show immunological dysregulation for several years after bereavement (9), including deficits in both their humoral and cell-mediated immune responses to influenza virus vaccine (10). With these issues in mind, we investigated immune responses to a bacterial vaccine and gave pneumococcal pneumonia vaccine to current caregivers, former caregivers, and noncaregiving control subjects.

MATERIALS AND METHODS

Subjects

For this study, we used 52 older adults (39 women, 13 men) who had never received a pneumococcal vaccine: 11 current spousal dementia caregivers, 13 former caregivers who had lost their impaired spouse an average of 2.08 ± 0.50 years before, and 28 noncaregivers (controls). These subjects were part of a larger longitudinal project on stress and health in older adults (7, 9). Subjects with immunologically related health problems such as cancer or recent

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surgeries were excluded. The Ohio State University Biomedical Research Review Committee approved the project; all subjects gave written informed consent before participation.

The three groups did not differ on sex, age, race, or education. Caregivers' mean \pm SEM age was 68.09 ± 3.80 , compared with 72.46 ± 2.29 for former caregivers, and 69.54 ± 1.69 for controls, $F < 1$, $p = .52$. The modal subject had completed several years of college; 84% were white. Caregivers spent a mean \pm SEM of 8.39 ± 1.98 hours per day in caregiving-related activities and reported that they had been providing care for 6.93 ± 0.94 years.

Psychological Data and Health-Related Behaviors

The 10-item Perceived Stress Scale (PSS) measured the degree to which subjects perceived their daily life during the prior week as unpredictable, uncontrollable, and overloading (11). Higher scores indicate greater stress.

The Interpersonal Support Evaluation List (ISEL) is a 40-item scale measuring perceived availability of four kinds of social support: appraisal, belonging, tangible, and self-esteem. The summary score includes the four scales, with higher values indicating greater support (12).

We collected health-related data to assess the possibility that caregiving-immunological relationships might simply reflect the contribution of other variables. Plasma albumin levels and body mass data provided information on the nutritional status of subjects. Questions from the Older Adults Resources Survey (13) assessed a wide range of health problems.

Vaccine, Timing of Samples, and Measure of Antibody Titers

The first blood sample was obtained just before vaccination, and subsequent samples were secured 2 weeks, 1 month, 3 months, and 6 months after vaccination. All blood samples were drawn between 8:00 AM and 11:00 AM to control for diurnal variation. The vaccine consisted of noninfectious bacterial polysaccharide capsular antigens (Merck & Company, Inc.). Pneumococcal-specific IgG titers were determined by ELISA.

Statistical Methods

Antibody data were subjected to log transformations (base 10) to normalize the distributions before analyses. Analysis of variance was used to assess differences among groups, change over time, and the interaction of these variables. Chi-square tests were used to analyze bivariate data. Throughout our data, we found no significant gender differences. Thus, although gender was included as a variable in earlier analyses, sex differences will not be reported.

RESULTS

Antibody Responses to Pneumococcal Pneumonia Vaccination

Vaccine responders were defined in the usual manner as those individuals whose antibody titers rose four-fold or more to the pneumococcal vaccine (3, 7); 39 participants (75%) had responded by 1 month. Comparisons of prevaccination antibody titers showed no differences among the three groups, $F < 1$, $p = .62$,

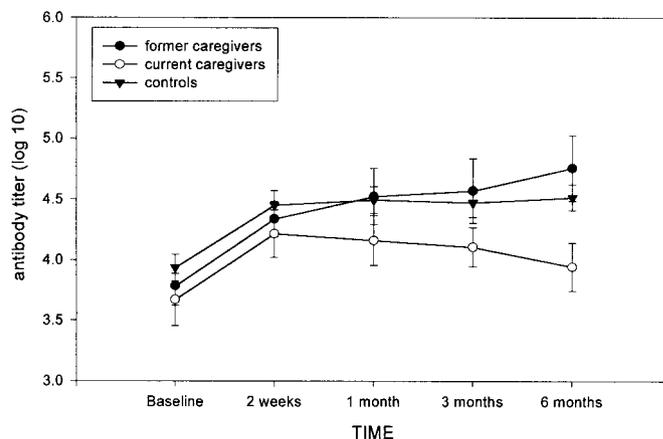


Fig. 1. Antibody responses to pneumococcal pneumonia vaccine (mean \pm SEM) before vaccination and 2 weeks, 1 month, 3 months, and 6 months after vaccination for current caregivers, former caregivers, and controls.

and no differences in the percentage of responders at either 2 weeks or 1 month, $\chi^2 < 1$, p values $> .78$.

Although antibody titers did not differ by group before or immediately after vaccination, the pattern of change over 6 months clearly differed, reflected in the significant group by time interaction, $F(5.82, 142.46) = 2.56$, $p < .03$, using the Geisser-Greenhouse adjustment. Caregivers' mean antibody titers diminished over time, while those of both former caregivers and controls remained stable (Figure 1). A secondary analysis, including only the 75% of subjects who responded to the vaccine by 1 month, showed the same significant group by time interaction, $F(6, 108) = 3.10$, $p < .01$, replicating the pattern of change among the three groups.

Psychological Data and Health-Related Behaviors

Group differences in self-report stress on the PSS at baseline were in the expected direction, although they did not reach significance, $F(2, 49) = 2.49$, $p = .09$; caregivers had a mean of 16.73 ± 2.82 , compared with 10.46 ± 2.44 for former caregivers and 9.61 ± 1.73 for controls. However, caregivers reported significantly less social support, $F(2, 49) = 3.55$, $p < .04$, with a mean for caregivers of 29.82 ± 2.98 , compared with 37.85 ± 1.67 for former caregivers and 36.57 ± 1.53 for controls. In accord with the majority of caregiving studies, caregivers' immune data were not reliably correlated with caregiving variables, including years spent caregiving, the number of hours per day consumed by caregiving activities, or the extent of patient impairment.

Health-related behaviors did not distinguish among the three groups. Only one control and two former

caregivers were smokers, and alcohol consumption was low and did not differ among groups, $F < 1$, $p = .72$. The three groups did not differ in body mass, recent weight change, sleep in the last 3 days, or exercise, all F values < 1.11 , p values $> .37$. All participants had plasma albumin levels within normal range.

The majority of older adults take some medication; in our sample, the most commonly used medications were estrogen ($N = 11$), diuretics ($N = 10$), calcium channel blockers ($N = 9$), cholesterol-lowering drugs ($N = 9$), beta blockers ($N = 7$), thyroid supplements ($N = 7$), and nonsteroidal anti-inflammatories ($N = 7$); in each case, use was distributed among groups, and there were no significant concentrations within any single group.

Similarly, comparisons for each of the health problems from the Older Adults Resources Survey (13) did not produce even marginal differences for any category, and the sum of endorsed problems did not differ among groups, $F < 1$, $p = .37$. Thus, we found no reliable differences in health-related behaviors among groups that would have accounted for the immunological differences.

DISCUSSION

We found that IgG antibody titers to the pneumococcal vaccine fell over a 6-month period in the caregivers, whereas antibody titers were stable in the control and former caregiver subjects. These data suggest that stress did not interfere with the initial antigen processing phase of the immune response to the vaccine. This interpretation is consistent with a previous report that examined the impact of stress on the immune response to a pneumococcal vaccine in children. In that study, the authors did not find relationships between ratings of problem behavior and antibody responses to six vaccine antigens (14). Indeed, the findings of Boyce et al. (14) are consistent with the absence of initial differences in vaccine response among our groups; it was only by following caregivers over time that the group differences in antibody titers became apparent.

The antibody response to a pneumococcal vaccine is thought to be a primary immune response. Unlike the primary immune response to a viral vaccine that has a T cell-dependent component, the primary immune response to bacterial polysaccharides is T cell independent. Thus, a pneumococcal vaccine does not generate memory B cells. In addition, the vaccine made by Merck contains bacterial polysaccharide capsular antigens that are different from antigens of strains of bacteria generally found in the population (Dr. Paul Beninger, Merck & Co. Inc., personal communication).

There are at least two possible explanations for the data found in this study. First, the physiological changes in the immune response induced by chronic stress resulted in a decrease in the number of IgG-producing B cells. The second possibility is that the number of IgG-producing B cells remained the same, but the B cells in the caregivers were not able to maintain the synthesis of IgG over time, as compared with the controls and former caregivers.

The finding that caregivers' antibody titers decline over time is important because pneumonia and influenza are together the fourth leading cause of death among individuals 75 or older (8, 15). Thus, these data complement and extend prior studies on caregivers' impaired response to influenza virus vaccine (3, 7), and provide the first evidence that chronic stress can affect the stability of IgG antibody levels to a bacterial vaccine over time.

The immunological decrements associated with the stress of caregiving are of particular concern because older individuals already have age-related reductions in cellular immune function with important health consequences: respiratory infections such as influenza and pneumonia remain major causes of morbidity and mortality among older adults (8). Adults who show poorer responses to vaccines and other antigenic challenges also experience higher rates of clinical illness, including influenza virus infection (8). These data provide additional evidence that caregiving increases the risk for morbidity and mortality among older adults (1) at least in part through maladaptive alterations in the immune response (15).

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