Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination

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Summary

Background There are many reports of psychological morbidity in spousal carers of patients with dementia. The consequences of this increased stress on the immune system are unclear. We investigated whether antibody responses to influenza vaccination differed between carers and a control group, and the relation of the antibody response to the hypothalamic-pituitary-adrenal (HPA) axis.

Methods 50 spousal carers of dementia patients, median age 73 years (IQR 66–77), and 67 controls (68 years [66–71]) of similar socioeconomic status were enrolled. Anxiety and depression were measured by the Savage Aged Personality Screening Scale and stress by the Global Measure of Perceived Stress scale. Principal-component analysis was used to yield a summary score of emotional distress from these two scales. Salivary cortisol concentrations were measured over a single day at three times (0800–1000, 1100–1300, and 2000–2200). Participants received a trivalent influenza vaccine and IgG antibody titres to each strain were measured on days 0, 7, 14, and 28.

Findings Mean scores of emotional distress were significantly higher in carers at each time point than in controls (all p<0.0003). Mean (SD) salivary cortisol concentrations, calculated as area under the curve (AUC), were higher in carers than controls at all three assessments (6 months 16·0 [8·0] vs 11·2 [4·4], p=0.001; respectively). Eight (16%) of 50 carers and 26 (39%) of 67 controls had a four-fold increase in at least one of the IgG titres (p=0.001). There was an inverse relation between AUC cortisol and IgG antibody titre to the Nanchang strain that was significant on day 14 (r=-0.216, p=0.039).

Interpretation Elderly carers of spouses with dementia have increased activation of the hypothalamic-pituitary-adrenal axis and a poor antibody response to influenza vaccine. Carers may be more vulnerable to infectious disease than the population of a similar age.

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Introduction

The task of caring for a significant other with a dementing illness is arduous and prolonged. Furthermore, the care of people with dementia is generally by partners who are themselves elderly and often ill-prepared for the physical and emotional demands placed on them. There are many reports of increased psychological morbidity in carers which, according to some investigators, may persist for up to 2 years after the partner is taken into full-time care.

The consequences on the immune system of this increased stress have been investigated but both the existence of immune impairments and the significance of the specific deficits are controversial. Impairments in T-cell proliferation in response to mitogens, shift in T-cell subpopulations, and reductions in natural killer cell in vitro provide little information about the clinical significance of the observed immune alterations. To know whether chronic stress increases vulnerability to disease in the elderly, the immune assessment must be both specific and involve exposure to a clinically relevant in vivo antigenic challenge.

Kiecolt-Glaser and colleagues found that spousal carers of dementia patients had a poorer antibody response to influenza vaccination than non-carers matched for age and sex. Other workers have suggested that neuroendocrine mechanisms may account for the inverse relation between stress and immunity.

Bereaved women have reduced natural-killer-cell activity and increased plasma cortisol concentrations. Similarly, psychiatric inpatients who described themselves as more distressed and isolated had higher concentrations of urinary cortisol which were associated with poorer proliferative responses of T cells to the mitogen phytohaemagglutinin and reduced natural-killer-cell activity.

We investigated the immune response to influenza vaccine and the activity of the hypothalamic-pituitary-adrenal (HPA) axis in spousal carers of dementia patients and non-carers. We hypothesised that spousal carers of dementia patients would have poorer antibody responses to influenza vaccine and persistently elevated concentrations of cortisol in the 6 months before vaccination compared with controls.

Methods

Patients

This investigation was approved by the ethics committee of the United Bristol Healthcare Trust and the Frenchay NHS Trust. All participants gave informed written consent. 50 spousal carers (24 men) of patients with dementia were recruited from the Bristol Memory Disorders Clinic where their partners had attended. The inclusion criteria were: a partner with a diagnosis of dementia; they were the primary carer; and that they cared for their partners at home and reported no other caregiving responsibilities. 67 controls (31 men) were recruited from a...
The psychological data were scored by the Formic electronic symptom, social anxiety, and life-event scores. 1 4 1 5 1 6 on factor 1 and 0·22, 0·03, and 0·23 on the remaining three for the anxiety and depression subscales are 0·76 and 0·47, respectively. The scale also correlates with measures of depressive symptoms, social anxiety, and life-event scores. 1 9 In addition to the robust psychometric characteristics of these scales, the Savage Aged Personality Screening Scale was deemed appropriate for this study since it has been designed specifically for use with elderly people. 1 5 , 1 6 For the Savage Aged Personality Screening Scale and stress by the Global Measure of Perceived Stress has been extensively used in the stress literature. 4 5 2 1 HPA axis Cortisol is increased with stress and thus, provides an objective marker of stress-induced HPA-axis activity. 7 2 0 Salivary cortisol correlates well with plasma cortisol, 7 2 3 avoids venepuncture-associated stress, and remains stable for several days. Saliva was collected using salivettes (Staredt, Leicester, UK). Participants were asked to collect three saliva samples over a single day; between 0800–1000 (before breakfast), 1100–1300 (before lunch), and 2000–2200 (at least 2 h after the evening meal). Sampling times were chosen to avoid the confounding effects of food intake and diurnal rhythm, and to maximise the detection of individual differences. Samples were collected 1–2 days before the follow-up meeting and were kept refrigerated until then. Upon arrival in the laboratory, the sample was frozen. Thawed saliva samples were spun at 3000 rpm for 15 min. 25 µL of sample was added to wells which contained 75 µL buffer (0·02 mM sodium citrate, 0·049 mM sodium dihydrogen orthophosphate dihydrate, and 0·1% bovine serum albumin; pH 7·2–7·4, 50 µL antibody (Bioclin Cortisol-3-OCMO, Bioclin, Cardiff, UK), and 4000–5000 cpm iodine-125 cortisol (Amersham, UK). All samples were run in duplicate. The plates were then mixed and left to incubate overnight at 4°C. 100 µL charcoal was then added to each well before spinning at 3000 rpm for 15 min. Equal volumes of sample and Optiphase Charcoal charcoal was then added to each well before spinning at 3000 rpm for 15 min. Equal volumes of sample and Optiphase Charcoal.
Figure 1: Salivary cortisol concentrations

Monoblend viruses were made by inoculating eggs with a working seed of each strain. Eggs were incubated and the allantoic fluids harvested, clarified, and inactivated before being concentrated into pooled zonal concentrates. A splitting process was used to release the surface antigens; these were separated by sucrose-gradient centrifugation. The haemaglutinins and nucleoproteins were filtered sterilised to produce a Monoblend of each strain, diluted in coating buffer, and incubated at 4°C overnight. The plates were washed with wash buffer, 100 µL blocking buffer was added, and incubated at 37°C for 1 h. Blocking buffer was removed and the plates washed three times. A combination of three samples with high values were the positive quality controls. Samples and controls were run in triplicate. All samples were plated out in doubling dilutions from 1/100 to 1/3200 (final volume=100 µL/well). Plates were incubated for 2 h at room temperature and then washed three times. The bound human IgG antibodies were detected by an alkaline-phosphatase-conjugated goat antibody specific for human IgG Fc (ICN Biomedicals GmbH, Eschwege Germany) diluted to a concentration of 1/1000. The plates were developed by addition of nitrophenol phosphate (Sigma-Aldrich, Poole, UK) 100 µL/well and the reaction stopped by 50 µL 3N sodium hydroxide. The optical densities were then read at 405 nm on a microplate reader (Bio-Rad Laboratories, Hemel Hempstead, UK).

Data from the 1/200 dilution were the most sensitive and, therefore, were used in the analyses. Individuals whose day 0 antibody concentrations to the Harbin, Johannesburg, or Nanchang strains were equal to or greater than the positive controls were deemed null-responders and were excluded from the analysis because changes post-vaccination would not be detectable. A four-fold increase in titre was deemed a positive response.

<table>
<thead>
<tr>
<th>Viral strains</th>
<th>Harbin</th>
<th>Nanchang</th>
<th>Johannesburg</th>
</tr>
</thead>
<tbody>
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<td>Differences between groups</td>
<td>0.042</td>
<td>0.941</td>
<td>0.657</td>
</tr>
<tr>
<td>Differences over time</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Interaction between time and group</td>
<td>0.015</td>
<td>0.619</td>
<td>0.919</td>
</tr>
</tbody>
</table>

Table 3: Repeated measures ANOVA between groups over time by each viral strain

Statistical analysis

The frequency of several key illnesses at baseline were compared to ensure that the two groups did not differ by health status. All analyses were done by the Statistical Package for the Social Sciences (SPSS v 6.1). Between group differences in stress levels and salivary cortisol concentration were compared by oneway ANOVA. Repeated measures ANOVA were used to examine between group differences in antibody concentrations. Pearson’s product-moment correlation analyses were used to examine the relation between salivary cortisol concentrations and antibody concentrations. Differences in proportions between groups were compared by means of χ² test.

Results

The characteristics of the participants and their known disorders are shown in table 1. All participants were Caucasian. Mean (SD) scores of emotional distress were significantly higher in carers than controls at each time point in the 6 months before vaccination: at 0 months 0·43 (1·09) vs –0·31 (0·81); at 3 months 0·47 (1·00) vs –0·33 (0·86); and, at 6 months 0·39 (1·06) vs –0·29 (0·85), all p<0·0003.

Similarly, mean AUC values for cortisol were significantly higher in carers at each time point: at 0 months 17·8 (10·3) vs 13·6 (7·7), p=0·017; at 3 months 14·6 (9·2) vs 11·2 (4·7), p=0·012; and at 6 months 16·0 (8·0) vs 11·2 (4·4), p=0·001. Figure 1 shows the diurnal profiles of salivary cortisol concentration in carers and controls at the 6 month follow-up.

Antibody concentrations to any vaccine component did not differ between carers and controls at day 0 (table 2). Analyses of proportion of vaccine responders in each group showed that 26 (39%) of 67 controls had a positive response to at least one of the vaccine components compared with 8 (16%) of 50 carers over the 28 day follow-up period (p=0·007). Further analyses of the antibody response to each of the vaccine components were done excluding null-responders: Harbin strain (19 carers, 19 controls); Johannesburg strain (13 carers, 9 controls); and Nanchang strain (16 carers, 9 controls). Both carers and controls had significant increases in each antibody response over the 28 day follow-up (all p<0·0001). Carers, however, had a poorer response to the Nanchang strain than controls (p=0·042). There was a significant interaction between group and immune response over time to the Nanchang viral strain (table 3).

The profile of IgG responses to each viral component for carers and controls are shown in figure 2. The correlation between cortisol concentrations (ie, the mean of cortisol AUC scores at 0, 3, and 6 months) and the antibody responses were r=–0·192, p=0·069 on day 7; r=–0·216, p=0·039 on day 14; and r=–0·184, p=0·078 on day 28.
Discussion

We found increased levels of distress in carers of spouses with dementia compared with controls. This increased distress was also associated with significantly raised concentrations of cortisol. Furthermore, the chronic activation of the HPA axis was associated with significantly impaired antibody responses to influenza vaccination. The proportion of carers who were able to generate a four-fold increase in antibody titre to at least one of the vaccine components was substantially lower than that observed in controls. This is similar to the results from Kiecolt-Glaser and colleagues who reported that only 38% of their carers had a four-fold increase in antibody titre, compared with 66% of controls.

We found that significantly impaired immune responses were only evident in response to one of the three viral strains. This apparent anomaly may suggest that the side effects of stress on immune function are not pervasive and that this, in turn, reduces the clinical relevance of stress-related changes in immune function. However, the absence of differences between carers and controls in their IgG responses to the Johannesburg and Harbin strains may have been a consequence of a recent exposure to these viral strains. Both the Johannesburg and Harbin strains were included in the 1996/97 vaccine preparation (ie, the vaccine used in the year before this investigation) there is, therefore, a greater likelihood that participants had been exposed to these viral strains recently—either by vaccination or natural exposure. Hence, antibody responses to the Johannesburg and Harbin strains in the vaccine may have been more robust than those produced to the Nanchang strain, and may have obscured between-group differences.

The correlation between the antibody concentrations to the Nanchang viral strains on days 7, 14, and 28 and the mean AUC salivary cortisol concentration were consistently negative which suggest an inverse relation between the immune response and HPA activation. Other investigators have also found an association between stress and poor immune function. We identify chronic hyperactivation of the HPA axis as one of the pathways that may be mediating the observed relation between chronic stress and immune dysfunction in this group.

Further studies will be needed to show causality. Our cohort of controls were recruited after an advertisement in a local newspaper and this may have led to a bias in this sample associated with motivational factors. Despite this, we feel that the differences we have shown in psychological status, neuroendocrine status, and immunological response are unlikely to be a result of cohort selection.

In view of the increased morbidity and mortality in elderly groups after exposure to influenza viruses, our findings may be of clinical relevance. The prophylactic benefits of vaccination depend on the host’s ability to generate a four-fold increase in antibody titre. Our data suggest that chronically stressed elderly individuals may be at higher risk from viral disease because of an inability to mount this “appropriate” immune response.

Contributors
K Vedhara, GK Wilcock, SL Lightman, and NM Shanks are responsible for the design and funding of the study. K Vedhara and GK Wilcock recruited the participants and, along with M Hunt, did the follow-up. N Cox and P Perks did the laboratory assays. K Vedhara and S Anderson analysed the data. All authors were involved in the preparation of the manuscript.

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References


