

IMMUNOLOGIC CHANGES IN ALZHEIMER CAREGIVERS

Janice Kiecolt-Glaser, Ph.D.

Introduction

Thus far, the presentations have focused on individuals with specific diseases in revealing a link between psychological variables, stress, and changes in the immune system. But changes associated with emotional distress can also impact upon the immune system of individuals without serious disease. Dr. Janice Kiecolt-Glaser has conducted research demonstrating that those who care for parents or for spouses suffering from long-term illnesses such as Alzheimer's disease manifest changes not only in specific cell types within their immune system, but also in their ability to produce antibodies after vaccination. She is a Professor of Psychiatry at Ohio State University and a scientist who is nationally recognized for her contributions to the field of PNI. During the course of her research with Alzheimer caregivers she has also found that the immune system responses that are affected can persist as long as three years after the death of a spouse. Thus, in gaining an understanding of how psychological variables may influence the course of disease susceptibility, it is necessary to examine not only those events immediately preceding the changes in susceptibility, but to examine events that might have occurred several years earlier.

Examination Stress and Immunity

Before I begin, I would like to acknowledge my collaborator and husband, Dr. Ronald Glaser of the Department of Medical Microbiology and Immunology at Ohio State University, who has worked with me on these studies since 1982. I am also indebted to Dr. John Sheridan from Ohio State University, who is responsible

for performing the flu assays that are an important part of our newest study, which I will be describing.

In 1982, Ron and I began collaborating on a series of studies with medical students that spanned a ten year period, and those studies provide important background information for the work I will be describing. Every year for ten years, we studied our medical students at Ohio State University, which has an absolutely marvelous paradigm for studying stress. It is based upon the fact that exams are grouped into three-day periods. Consequently, we can follow students in their pre-clinical years during periods of low stress and then during exams. We can watch across the academic year as we follow them through low and high stress periods, and assess changes in a very large number of different immunological components.

One of our most recent studies was designed to determine if the stress of examinations might alter the students' immunologic response to a vaccine. It was felt that these studies would provide very important data for us in the context of a 'real world' situation. When you meet a new antigen, does stress alter your ability to respond to that new antigen? Hepatitis-B vaccine was administered in the standard way, except that we made sure that inoculations coincided with the student's examination blocks. Thus, they were subjected to a stressor simultaneously with exposure to the vaccine.

We found that between the first and second inoculation, 12 of the 48 students sero-converted, i.e., developed measurable antibody to hepatitis-B. Interestingly, those 12 students were significantly less stressed and less anxious than their fellow students (the remaining 36 who did not respond to the vaccine challenge). When we followed them out at six months, we found that in addition to reduced stress, students who had an improved response to the vaccine also reported more satisfying personal relationships. This was correlated with higher antibody titers as well as enhanced T-cell immunity.

Stress Associated With Caregiving

Those were very interesting data, but we wondered what would happen with very long term, enduring, and chronic stress. Alzheimer's disease, as you may well know, provides such a model: the family members who are taking care of an Alzheimer's patient experience chronic stress. The etiology of Alzheimer's disease is unknown, and the course is quite unpredictable. It may range from a few to as long as 20 years until the patient eventually dies. The disease is uncontrollable with no effective treatment. The following anecdote underscores the difficulties that Alzheimer caregivers face. Mr. M is a retired engineer who had been caring for his wife at the point we saw him for about five years. He told us how in the past, he and his wife had spent summers at a cabin they owned on an island in a lake. That year, his wife had had a sharp decline in cognitive function, and she was really confused when they started to go to the island by boat. When she reached the island, she became very confused, she didn't recognize her husband, and she ran screaming from him, yelling that he was trying to mug her. Mr. M was fortunate in that the people on the island knew him well, and knew his wife well, so they were able to calm her down and bring her back. But he was very distressed by the incident because, as he phrased it, "It seems I can never take her out again in public, because I can't risk something similar happening in a circumstance where they don't know me and they don't know her. I don't know what would happen to either of us in those circumstances." So his life became increasingly circumscribed and increasingly stressful after that time.

We first asked our caregivers how long they had been providing care. The average time was between five and six years, but the range was anywhere from a year or less to 20 years. So these are not new caregivers at the inception of the study that I am talking about.

Immunologic Changes in Caregivers

Another goal of this study was to follow the caregivers beyond the death of the Alzheimer's patient. We thought that this model could provide a good way to examine the effects of a naturally occurring chronic stressor. After the person adjusted to bereavement, perhaps a year, studies reveal that you generally don't observe the same intensity of anxiety and depressive symptoms. By that time, we thought that we might begin to see some return in immune function. When a woman wrote to us saying, "Do you want to keep me in the study? My husband died two months ago and I'm not sure if you still want me in the study, because I am no longer a caregiver?", we assured her that we did want her in the study.

When we started looking at some data in year five of the study - and this is from Brian Esterling, who is a post-doctoral fellow in Ron's laboratory - we first looked at natural killer cell activity in the first 61 subjects who happened to be evaluated within a several month period. There were no differences in natural killer cell activity as a result of being a 'continuing caregiver' or what we're going to be calling 'bereaved caregiver', though an average of two years has elapsed since the death of their patient. That is not surprising. Two other laboratories, including Mike Irwin's in San Diego, and Peter Vitaliano in Washington, have also failed to find differences between caregivers and control subjects in natural killer cell activity. But Ron decided to look at the augmentation of natural killer cell activity by two cytokines, first using interferon-gamma. When we looked at the natural killer cell response to augmentation by this cytokine, we found that there was very clearly a difference between caregivers and control subjects. The controls were responding better, and the continuing caregivers did not improve. It is important to note that the two groups here did not differ at all in terms of age, in terms of education, or proportion of women. We found much the same pattern when we assessed the effects of augmentation with interleukin-2 (IL-2). However, there were no differences between continuing and bereaved caregivers, but both were clearly doing more poorly than our control subjects in terms of natural killer cell responsiveness to augmentation.

Vaccine Responsiveness of Caregivers

One of the obvious questions is whether there were any differences in health behaviors. That is something we always assess every time we see people and draw blood. For example, caregivers sleep less and eat less well than controls. If you know anything about caregiving and the stresses of caregiving, you wouldn't be surprised to hear that. We did not find any other reliable differences in health behaviors between the groups. We also failed to find significant or reliable correlations between sleep and our immunological data. Next, we wanted to try a vaccine study using our caregivers as well, and examine the possibility that caregivers and controls might differ in their responsiveness to an antigen, in this case, to the influenza vaccine. We were in a transition period with grants, so we looked at people we already had in the sample, which in this case were spouses as opposed to children. The study included 75 controls and 49 caregivers. Controls and caregivers didn't differ at all in terms of age or proportion of women.

But the caregiving sample wasn't all we might have wanted in terms of having a really stressed caregiving sample. They actually rated themselves as somewhat less depressed in the prior year, and our controls, for unknown reasons, were rating themselves as somewhat more depressed, although the groups still did differ significantly. Moreover, 26 of those caregivers were former caregivers and had not been caregiving for an average of two years. Of the 23 continuing caregivers, only 11 still had their patient at home. Another 12 patients were now in a nursing home. Even worse for us was learning that the caregivers had been much better about getting flu shots. So we weren't optimistic about what we might find in this trial balloon. In fact, we were quite surprised by what we did find.

We first looked at antibody to the vaccine as measured by an enzyme linked immunoassay (ELISA). What we found was that even though our caregivers had a better vaccination history, they

had lower antibody titers, even at the point before vaccination. When we vaccinated them and then followed them for 10 to 14 days, we found that caregivers were still lagging behind controls in terms of their antibody response. This was a surprising finding. We had been talking with someone about this at a site visit, and one of the people at the site visit said, "That doesn't really count. What you really need to know is the T-cell response. That is the real gold standard." We disagreed, but John Sheridan had already made plans to do some follow-up examining the T-cell response so we carried out those assays. Was it only an anomaly in terms of the antibody response, or were there going to be T-cell differences there as well? At time zero, the groups didn't differ. Ten to 14 days out, everybody was responding very well and there were no significant differences. But when we followed the subjects for three months, when you hope to see the IL-2 response to a component to the vaccine in vitro maintained at as high a level as possible, we found that our caregivers were not doing as well as our control subjects. Again, we found no difference at all between our former and our continuing caregivers.

These data are very important in terms of public health. Pneumonia and influenza together are the fourth leading cause of death in people over 75 years of age. The immune response declines with age. It is one of the reasons why older adults are told to get flu vaccinations. Yet we find in terms of immune responsiveness at least to this antigen, that chronic and long term stress appears to decrease the effectiveness of the vaccine.

Psychological Variables

There is one other thing that we don't know and hope to be able to tease out over the next few years. That is the issue of what exactly is happening in our former caregivers. We have high rates of syndromal depression and anxiety disorders in our caregivers. We know in following people out through five years of the study that approximately 55 to 60 percent of our caregivers will meet

syndromal criteria for an anxiety or depressive disorder during the years that they are caregiving. We also know from lifetime assessments that we carry out when we first see the caregivers and controls that the two groups do not differ prior to the point of caregiving. What that reveals in terms of the stress of caregiving is that caregiving is sufficient to induce anxiety and depressive disorders in older adults with no prior history. Furthermore, at the outset of the study, we predicted that our former caregivers would be less symptomatic after they stopped caregiving. To the contrary, we found that after an average of two years following caregiving, there were no differences in rates of syndromal depression between the two groups. There is no diminution two years after caregiving has ended.

Conclusion

One possible explanation for our data is that we were simply observing a group that continues to be depressed and anxious, but we don't think that that is the entire story. When examining the standard errors between our continuing and our former caregivers, there was no great difference; we weren't seeing an inordinate amount of variability among our former caregivers which might suggest that this interpretation is correct. However, there is another alternative hypothesis, not inconsistent with these data, which we think may be very important. Studies by David and Suzanne Felten from the University of Rochester have examined the plasticity and recovery from stress in young and old animals. They have found that young and old animals are quite different in terms of their recovery. The older animals don't seem to have the same plasticity in terms of recovery. Thus, it is possible that chronic stress, especially in an older adult population, may serve to age the immune response, to accelerate the process of aging in ways that may or may not be recoverable.

DISCUSSION

Question: You mentioned the aging process as being enhanced. Did you do any studies comparing young versus older caregivers?

Dr. Kiecolt-Glaser: Originally, when we first started this series of studies, we had both spousal and offspring caregivers. Our offspring caregivers were on the average about 50 years old and the spouses were on the average 70 years old. The offspring do somewhat better, but it is also hard to say, because in terms of family life they are also different. The offspring caregivers were generally married, they had their own families, and they were enormously stressed by the experience. The spouses on the other hand had lost their major source of support and it had become their major source of strain. So it is hard to untangle what effects age may actually have on the process. We're hoping as we follow people over time to determine whether the age of the caregiver impacts on immune function.

Question: I'm wondering if any studies have been done on long term caregiving of parents with disabled children. I'm talking 15, 20, 25 years.

Dr. Kiecolt-Glaser: I know certainly that there have been a number of studies examining stresses on the families of parents who have disabled children and also of families who have children or other family members with severe mental disorders. My knowledge of that literature, which is certainly limited, is that no immunological studies have been done in those situations.

Question: In terms of your study, have you thought about including in the future, cultural aspects that may perhaps play a role? For example, certain groups in which the caregiving of elderly family members is incorporated in a particular culture that may have an influence in terms of the level of stress?

Immunologic Changes in Alzheimer Caregivers

Dr. Kiecolt-Glaser: I think that is an excellent question. We have been trying to recruit in Columbus a sample of African-Americans to help answer that question. What I do know, however, from Bill Haley at the University of Alabama, who has a sizable sample of African-American caregivers, is that there does appear to be a very different response. In a brief discussion with him, he said, if I understood it correctly, you do not see the same high levels of stress among African-Americans, because the family unit is much tighter knit and care of the elderly is more of a family responsibility. Consequently, the stress is less.