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Stress, Loneliness, and Changes in Herpesvirus Latency

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This study used a prospective design to examine the influence of examination stress and loneliness on herpesvirus latency as measured by changes in antibody levels to three herpesviruses, Epstein–Barr virus (EBV), Herpes simplex *type I (HSV-1), and cytomegalovirus (CMV). Three blood samples were obtained from 49 first-year medical students, with the first sample drawn 1 month before final examinations, the second on the first day of final examinations, and the third during the first week after their return from summer vacation. A median split on the UCLA Loneliness Scale divided subjects into high- and low-scoring loneliness groups. There were significant changes in the antibody titers to all three herpesviruses across the sample points, with the lowest levels found in the third (low stress) sample. High-loneliness subjects had significantly higher EBV antibody titers than low-loneliness subjects. These data suggest that stress-related immunosuppression can significantly modulate herpesvirus latency.*

KEY WORDS: psychoimmunology; herpesvirus; loneliness; stress.

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INTRODUCTION

There is growing evidence that major life changes can influence the incidence and course of illness through their impact on the immune response. For example, it was recently shown that natural killer (NK)-cell activity declined significantly in medical-student blood samples taken before and during examinations (Kiecolt-Glaser *et al.,* 1984a). Natural killer-cell activity is thought to be important in tumor surveillance, as well as in the control of virus infections. Two other factors were significantly related to NK activity, stressful life events and loneliness, with high scorers on both having significantly lower levels of NK activity. Similarly, in a sample of newly admitted nonpsychotic psychiatric inpatients, the high-loneliness subjects had significantly lower levels of NK activity, as well as a significantly poorer T-lymphocyte response to mitogen stimulation, than the low-loneliness group (Kiecolt-Glaser *et al.,* 1984b). These data are consistent with animal research (Monjan, 1981; Laudenslager *et al.,* 1983) and the limited human literature (Bartrop *et al.,* 1977; Jemmott *et al.,* 1983; Palmbald *et al.,* 1979) documenting the responsiveness of the immune response to psychosocial influences.

Considerable anecdotal speculation has linked stress and the appearance, duration, and intensity of herpesvirus infections, with such effects presumably reflecting alterations in cellular immunity. Previous studies have found an increased risk for infection by Epstein–Barr virus (EBV) in West Point cadets associated with certain psychosocial risk factors [high levels of motivation, poorer academic performance, and having a father who was an overachiever (Kasl *et al.,* 1979)]. In another study, Luborsky *et al.* (1976) found that general unhappiness among student nurses was predictive of the frequency of herpes labialis lesions. It is thought that such effects may be related to cellular immune competence.

The role of immunity in controlling the recurrence of latent herpesvirus infections is not well understood. Normally, after an active herpesvirus infection, virus is repressed in a latent state within specific host cells. Individuals who are immune suppressed often show increases in antibody titers to one or more of the herpesviruses, including *Herpes simplex* virus type 1 (HSV-1), EBV, and cytomegalovirus (CMV), presumably due to the humoral immune response to the increase in virus antigen(s) after reactivation. The cellular immune response is also thought to be important both for the limitation of the primary infection and controlling the expression of latent EBV (Klein *et al.,* 1981; Rickinson *et al.,* 1981). In some cases there are also severe clinical symptoms associated with reactivation of latent virus (Ho, 1977; Rickinson *et al.,* 1980; Harada *et al.,* 1982; Alford, 1981). Animal studies also have shown that induced immunosuppression reactivates latent HSV (Oakes *et al.,* 1980; Openshaw *et al.,* 1981).

In this study we used a prospective design to assess possible stress-related changes in herpesvirus antibody titers, which would presumably reflect modulation in the cellular immune response's control of latent virus. Blood samples and questionnaire data were obtained from first-year medical students 1 month before final examinations, on the first day of final examinations, and on their return from summer vacation. The presence of antibody to EBV, CMV, and HSV was assessed. Self-report distress data were collected concurrently from subjects in order to assess independently the stressfulness of the three sample points. A loneliness questionnaire was also included, since there is evidence that the subjective quality of interpersonal relationships may have important consequences for health (Wallston *et al.,* 1983).

METHOD

Subjects and Timing of Specimens

The subjects were 76 first-year medical students at The Ohio State University who volunteered for participation in research on stress and the immune response. Of these, 70 were present at all three data collection points. Insufficient plasma was available for analysis on nine subjects. Twelve of the remaining subjects were EBV seronegative, i.e., they did not have antibody to EBV, leaving a total of 49 subjects for the EBV analyses. The average age of the 16 women and 33 men was 23 years.

The first blood sample was obtained 1 month before final examinations, at the end of April. The second sample was drawn on the first day of final examinations at the end of May, and the final sample was collected during the first week in September, when the students had just returned from summer vacation. All blood draws were scheduled during the middle of the day. Self-report data were collected during the same period when blood was drawn.

Self-Report Measures

The Brief Symptom Inventory (BSI), a short form of the Symptom Checklist-90, was included to provide an independent assessment of the relative degree of distress associated with each of the three sample points (Derogatis and Spencer, 1982). Subjects rated of 53 items from 0 to 4, based on the amount of any associated discomfort during the last week.

The UCLA Loneliness Scale (Russell *et al.,* 1980) was included during the first data collection in late April to provide a brief subjective measure of

the overall adequacy of interpersonal contacts. Scores were divided at the median, 34.5, to form high (mean, 41.62)- and low (mean, 28.6)-scoring groups.

Subjects were also asked to list any recent health problems they had experienced in the 2 weeks prior to the collection of the second and third samples. Also, subjects were asked during the fall data collection (a) how many days, if any, they had been unable to pursue normal activities because of illness between the last two samples; (b) if they had a history of recurrent cold scores; and (c) if they had had any cold sores during the summer.

Cell Lines

The Burkitt lymphoblastoid cell lines, HR-1 and Raji, were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum, 25 μg/ml gentamicin, and 0.025% sodium bicarbonate. The cells were maintained at 35°C in 16-oz glass bottles. Primary human embryo lung (HEL) fibroblast cells were grown in Eagle's medium at 37°C.

Immunofluorescence Assay

The indirect immunofluorescence (IF) assay was used to measure antibodies to EBV antigens (Glaser *et al.*, 1973). The early antigen (EA) antibody titers were determined using Raji cells, superinfected with the lytic strain of EBV (HR-1) 24 hr postinfection in the presence of 5 μg/ml cytosine arabinoside, according to methods previously described (Henry *et al.*, 1978). Under these conditions, only EA is expressed. The virus capsid antigen (VCA) antibody titers were assayed using smears of HR-1 cells. Cells were fixed in acetone at room temperature for 10 min, adsorbed with twofold dilutions of plasma prepared in phosphate-buffered saline (PBS), pH 7.4, for 30 min at 37°C. The cells were washed with PBS and readsorbed with goat anti-human IgG conjugated to fluorescein isothiocyanate (FITC) for 30 min at 37°C. The cells were washed with PBS, counterstained with Evans blue, mounted in Protex, and examined with a Zeiss uV microscope. Antibody titers to EA and VCA were determined by the highest dilution of plasma still able to demonstrate IF-positive cells. All slides were read blind coded.

The Enzyme-Linked Immunoadsorbance Assay (ELISA)

To examine antibody titers directed against HSV and CMV, we used the ELISA assay. Human embryo lung cells were infected with either HSV-1

at a multiplicity of 5 to 10 plaque-forming units (PFU)/ml or CMV at 1–3 PFU/ml. Cells were maintained at 37°C until the cells showed an extensive cytopathologic effect (CPE). The cells were harvested, pooled, and used to prepare the antigen for the ELISA. Infected cell suspensions were washed three times with PBS, pH 7.4, and stored at −80°C until used.

In preparation for the ELISA, the cells were frozen and thawed three times. The cell suspensions were centrifuged at 750*g* for 15 min, after which the supernatants were removed and the pellet was discarded. A protein assay (Bio-Rad) determined the amount of protein present. Each antigen harvest was titrated to determine the optimum concentration of protein to use in the ELISA. Freshly prepared antigen was added to 96-well plastic Linbro plates (0.3 ml/well). The plates were incubated at 4°C overnight to allow the soluble antigen to adsorb to the plastic. Residual antigen was removed from each well, and each well was washed with buffer three times for 2 min. Then, 0.3-ml plasma dilutions were added to the test wells. Previously characterized HSV-1$^+$ or CMV$^+$ human sera were used to titrate each antigen as a control. In addition, an HSV-1$^-$ or CMV$^-$ serum, as well as PBS, was always used for a control. After the plasma dilutions were added to the wells, the plates were incubated at room temperature for 1.5 hr. The wells were washed three times with PBS. At this point, 0.3 ml of goat anti-human IgG was added to each of the wells. The plates were incubated at room temperature for 2.5 hr, after which the unadsorbed antibody was aspirated. The wells were washed three times with PBS. Then, 0.3 ml of 2-2-azino-di-3-ethyl-benzthiazolin sulfonate (ABTS), to which 3% hydrogen peroxidase had been added, was placed in each well. A dark-green color change indicated a positive reaction. The plates were read visually after 15 min, and the highest dilution of antibody detected to HSV-1 or CMV was determined by color change.

RESULTS

Virus antibody titers and self-report data were analyzed using a 2 × 3 repeated-measures analysis of variance design, with one between-subjects variable (low versus high loneliness) and one within-subjects variable (change over the three sample points). No significant effects were found when sex was included as an independent variable in the preliminary analyses, so data for both sexes were subsequently combined.

Self-Report Data

Self-report data, shown in Table I, provided confirmation of the presumed differences in distress associated with the three sample points.

Table I. BSI Means for the Three Sample Points

	Sample		
	1	2	3
Somatization*	49.51	53.24	48.35
Obsessive-compulsive symptoms***	58.33	63.90	53.45
Interpersonal sensitivity*	58.79	57.39	54.92
Depression***	56.88	59.47	53.92
Anxiety***	56.45	67.45	55.59
Hostility***	51.92	58.90	53.10
Phobic anxiety[a]	53.88	54.49	53.68
Paranoia[a]	52.41	53.62	52.90
Psychoticism**	57.03	59.66	54.61
Global severity index**	52.76	55.24	50.14
Positive symptom total***	57.02	60.59	53.82
Positive symptom index***	54.55	59.37	49.98

[a]Nonsignificant.
*$p < 0.05$.
**$p < 0.001$.
***$p < 0.0001$.

The examination sample was associated with the most distress, followed by the baseline sample, with the lowest self-ratings of distress occurring after the students' return from summer vacation.

Only seven students reported health problems in the 2 weeks preceding the second (examination) sample. The problems they listed were limited to minor and transient complaints, e.g., allergies, stomachaches, etc. Only eight students reported any illness of sufficient intensity to preclude their involvement in their normal daily activities between the second and the third sample points, during their summer vacation. Of these, four students reported that they were ill 1 day, while the remainder reported periods of 2 to 4 days. Seven of the students said that they were prone to cold sores, and seven students reported having cold sores between the last two samples.

Herpesvirus Antibody Titers

Since the method of doubling dilutions had been used to obtain both IF and ELISA antibody titers, a base 2 logarithmic conversion was used to reduce variance for the statistical comparisons involving antibody titers (Armitage, 1971). However, for descriptive purposes the antilog of the arithmetic mean of the log titers, or geometric mean of the raw titers (GMT), is presented, to allow comparisons with previous seroepidemiologic data.

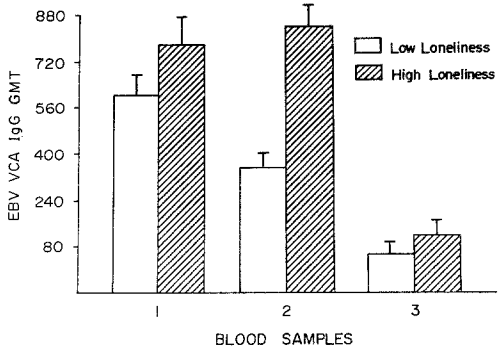

Fig. 1. Changes in the GMT (± SE) of EBV VCA IgG in high- and low-loneliness medical students across the three sample points.

There was a significant change in EBV VCA antibody titers across the three sample points [$F(2,94) = 42.81$, $P < 0.0001$], as shown in Fig. 1. The high-loneliness subjects had significantly higher VCA antibody titers than the low-loneliness subjects [$F(1,47) = 3.98$, $P < 0.05$]. The interaction between loneliness and change across sample points did not reach significance [$F(2,94) = 1.33$].

A total of 32 medical students had EA antibody titers of 1:10 or greater across all three bleeds and were, therefore, considered EA positive for inclusion in the EA data analysis. As with antibody to VCA, there were signficantly higher EA antibody titers associated with the high-loneliness group [$F(1,30) = 5.29$, $P < 0.03$]. The main effect for change in titers over sample points was nonsignificant [$F(2,60) = 2.20$, $P < 0.12$]. The interaction between loneliness and change over trials was not signficant ($F < 1$). These data are shown in Table II.

Due to the fact that plasma samples from all of these bleeds were used for several other assays for other studies, sufficient plasma was available only from blood samples 2 and 3 for a total of 30 subjects for the HSV and CMV antibody analyses. Of these, 28 students were positive for HSV antibody with titers of 1:10 or greater and were, therefore, included in subsequent analyses. There was a significant decrease in HSV antibody titers from the second to the third sample [$F(1,26) = 22.02$, $P < 0.0001$]. Only 1 subject had higher antibody titers on the third sample compared to the second, 5 had the same titer on both samples, and 22 had lower titers. The GMT was 361.20 for the second sample and 95.29 for the third. The main effect for loneliness was nonsignificant, [$F(1,26) = 1.37$], as was the interaction between loneliness and change over sample points [$F(1,26) = 2.90$]. While we used HSU-1 infected cells as the antigen, the specificity of the

Table II. Changes in the GMT (± SE) of EBV EA IgG in 32 High- and Low-Loneliness Medical Students Across Three Sample Points

	Low-loneliness GMT	High-loneliness GMT
Sample 1	47.11 (10.49)	137.56 (26.78)
Sample 2	84.11 (28.82)	99.17 (24.54)
Sample 3	49.83 (14.65)	68.83 (19.92)

HSV antibody titer (HSV-1 vs. HSV-2) is not known since there is cross-reactivity between the two strains. The changes in HSV antibody titer, therefore, may reflect changes in antibody to either or both strains.

Twenty of the 30 medical students tested had CMV antibody titers of 1:10 or greater on both samples and, therefore, were included in the analysis. The main effect for change over sample points was significant [$F(1,19) = 4.47$, $P < 0.05$]. The GMT was 21.72 for the second sample and 16.83 for the third. Loneliness was not included as a variable in this analysis, given the disproportionately small number of CMV-negative high-loneliness subjects.

In order to determine if the large changes in herpesvirus antibody levels reflected simply more general changes in plasma IgG, antibody levels to a recall antigen (poliovirus type 2) were also assayed. Poliovirus type 2 antibody titers were assessed using a standard neutralization assay on the 15 pairs of subjects for whom there was sufficient plasma remaining from samples 1 (baseline) and 3 (return from summer vacation). Insufficient plasma was available to include the second sample point; however, given the very elevated EBV antibody data for both VCA and EA IgG on sample 1 in contrast to sample 3, any comparable changes in poliovirus type 2 titer should still have been evident.

The poliovirus type 2 antibody titers did not change significantly ($F < 1$) over the two sample points, with a GMT of 14.13 on the first sample, compared to 12.27 on the third. Of particular importance is the fact that not 1 of the 15 subjects showed a difference of more than one dilution in either direction between the two samples, a difference consistent with the error of the test. In contrast, using data from the 11 subjects of the 15 tested for poliovirus type 2 antibody who were EBV positive, the VCA IgG antibody titer declined signficantly, from a GMT of 400 on the first sample to 107 on the third [$F(1,10) = 5.19$, $P < 0.05$].

DISCUSSION

Significant changes in EBV, HSV, and CMV antibody titers but not poliovirus type 2 were found in this medical-student group across sample

points. These data suggest that significant and measurable changes in the cellular immune response, as measured by changes in herpesvirus antibody titers in latently infected medical students, can be associated with commonplace stressors in an otherwise healthy population.

Consistent with previous data, significant effects were found for loneliness in the EBV antibody titers, with the high-loneliness subjects having significantly higher EA and VCA titers. We have now shown a significant association between loneliness and competency of the immune response across two very different populations, medical students and psychiatric inpatients, on four different direct or indirect measures of cellular immunocompetency (Kiecolt-Glaser *et al.,* 1984a,b,c). The consistency of these data strongly supports the hypothesized importance of interpersonal relationships for health-related outcomes (Wallston *et al.,* 1983; Cohen and McKay, 1984; Kiecolt-Glaser and Greenberg, 1984).

The very elevated EBV antibody titers on the first sample point suggest that there was already some compromise in cellular immunity at baseline, particularly in comparison to data from previous EBV seroepidemiological studies. Those studies have shown characteristic EBV VCA IgG GMTs of 1:80 and EA IgG GMTs of 1:10 or less in normal adult populations (Henle and Henle, 1982). The exceptions to these general serologic patterns have been documented in patients who are immunologically compromised, e.g., those with immunosuppressive diseases, those under immunosuppressive therapy, or those with Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC), two malignant diseases with which EBV is associated (Tuckwiller and Glaser, 1983). Elevated antibody titers in patients without malignant disease are thought to occur in response to enhanced expression of latent virus due to changes in, or dysfunction of, different T-lymphocyte subpopulations (Klein *et al.,* 1981; Rickinson *et al.,* 1981; Henle and Henle, 1982).

It is of interest that while antibody levels to EBV, HSV, and CMV (viruses with which the students were latently infected) were reactive to academic stressors, antibody to poliovirus type 2 remained stable. We analyzed antibody titers to poliovirus type 2 to help assess the possibility that the elevated herpesvirus antibody titers on the first two samples reflected simply more general changes in plasma IgG levels. Poliovirus type 2 was chosen as a recall antigen because its widespread use in school vaccination programs provided some assurance that most students would have antibody. Unlike the latent herpesviruses which are not eliminated by the immune system, the attenuated poliovirus used for vaccination does not induce a latent infection and is, therefore, cleared by the host immune response. The fact that large changes were observed in the herpesvirus antibody titers but not poliovirus antibody titers supports the hypothesis that the herpesvirus data reflect stress-related changes in virus latency.

The herpesviruses are multipotential, having the ability to produce multiple kinds of disease (Glaser and Gottlieb-Stematsky, 1982). Significant compromises in cellular immunity which allow increased viral production may have associated risks. For example, while HSV-1 is responsible for inducing common cold sores, it can also produce generalized infections, encephalitis, and death (Adam, 1982).

In individuals with a normal cellular immune response, primary CMV infections can produce a mononucleosis syndrome which usually resolves in 3 to 6 weeks (Sullivan and Hanshaw, 1982). However, in immunologically compromised patients, both the primary infection and infections resulting from reactivation of endogenous latent virus are often associated with high rates of morbidity and mortality. For example, CMV is the single major known cause of interstitial penumonia, the largest source of death in bone marrow transplants (Sullivan and Hanshaw, 1982).

Several laboratories have reported significantly higher herpesvirus antibody titers (HSV-1, CMV, varicella zoster virus) in psychiatric patients compared to nonpsychiatric controls; no differences have been found when other viral antigens such as measles or rubella were used (e.g., Lycke *et al.*, 1974; Halonen *et al.*, 1974). These data have led researchers to posit a possible etiologic relationship between certain psychiatric syndromes and the herpesviruses. However, the large stress-related changes in these medical student antibody data suggest that the differences between psychiatric patients and controls may reflect simply the greater distress in the former.

There has been considerable anecdotal speculation which has linked the occurrence of aversive events and the onset, intensity, and duration of human herpesvirus infections. The data from this study strongly suggest that relatively commonplace aversive events can be associated with signficant changes in herpesvirus latency. Data from other laboratories also support the importance of psychosocial variables as potent modifiers of immunocompetence, with such effects mediated through multiple pathways (Ader, 1980; Solomon, 1981; Coe *et al.*, 1984; Cohen-Cole *et al.*, 1981).[6]

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[6]In order to rule out that the changes in antibody titers to EBV were associated with an epidemic of EBV infections, we assayed for EBV VCA IgM antibody. Plasma from 15 subjects were selected at random from the first and third bleeds (paired) and assayed for this antibody. All plasma specimens were found to be negative for VCA IgM antibody, showing that there was no epidemic of EBV infections.

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