

Relationships Between Temperament and Immune Function in Children with AIDS: An Exploratory Investigation

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Abstract

While substantial evidence for psychoneuroimmunologic (PNI) relationships has accumulated within healthy adult populations, data regarding PNI effects in HIV-infected individuals is inconsistent, and PNI research in children – healthy or ill – is almost nonexistent. The present research explored relationships between emotional factors and immune function in 32 children who had been infected perinatally with HIV. Temperament subscales were combined to form two independent factors, a “negative” factor reflecting general emotionality. Six of ten partial correlational analyses performed were significant, with five of the six indicating enhanced immune status and function in connection with greater emotionality.

Introduction

Evidence that emotional factors are related to immune function has been accumulating for some years. While it seems to be generally the case that psychological depression and distress are connected with suppressed immune function, possibly mediated by corticosteroid production, other aspects of emotionality are associated with superior immunity¹. Specifically, emotional reactions involving sympathetic nervous system activity – for example, fear and anger – are often associated with increased numbers of lymphocytes². Studies designed to examine immunological effects of specific neuroendocrine mediators have similarly shown that catecholamines, which are released during sympathetic adrenal-medullary (SAM) activation, have some immunoenhancing effects^{3–6}, while hy-

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pothalamic pituitary adrenocortical (HPAC) activation and the consequent presence in serum of corticosteroids is immunosuppressive^{7,8}.

In HIV-infected individuals, these effects are less reliable and even inconsistent⁹. For example, distress has been observed in connection both with enhanced^{10,11} and with reduced^{9,12} immune activity. A possible source of this inconsistency resides in the fact that the period of exposure to the virus, a factor that may determine psychoimmunologic relationships at a single point in time is unknown in adults⁹. Results of one adult study suggest the dispositional sympathetic reactivity, operationalized as the degree of peripheral sympathetic activity evinced during emotional reliving, is associated both with superior immune function and with length of survival, controlling for disease status and CD4 lymphocyte numbers¹³.

Almost nothing is known about psychoneuroimmunologic relationships in children. One recent study has suggested that they may differ from those observed in adults. While depression is associated with impaired immune function in adults¹⁴, depressed children show enhanced lymphocyte response to mitogens¹⁵. A great need exists for exploring PNI phenomena across the lifespan.

One aspect of childhood emotionality is temperament, which is a rubric that encompasses phenomena such as irritability, activity level and fearfulness, and is thought to have heritable underpinnings^{16,17}. Neuroendocrine activity has been shown to be correlated with some aspects of temperament in several studies, with proneness-to-distress associated with enhanced HPAC activity¹⁸ and reactive emotionality (which encompasses both negative and positive emotions) associated with increased SAM responsiveness¹⁹.

The present study was an exploratory investigation of relationships between temperament and immune function in children with AIDS. In this study, period of infection – since it corresponds to the child's age – could be statistically controlled. Temperament information was obtained via interview-format assessment conducted with the primary caregivers.

Method

Subjects

Subjects were 32 children receiving medical treatment in central New Jersey for HIV infection confirmed according to the revised CDC system²⁰. The children's mean age was 3 years, 4 months, and ranged from 3 months to 11 years, 0 months. Of the 32 children, 28 had been infected perinatally, 1 had received a contaminated blood transfusion a few days after birth, and three were hemophiliacs who had required frequent infusions of factor from birth and may thus be assumed to have been infected soon afterward²¹. Nineteen of the children were male and 13 female. Of the 27 caregivers, 12 were biological mothers, 8 were foster mothers, and 7 were other relatives. It is very difficult to quantify over-

¹ Data were analyzed with and without inclusion of the hemophiliac subjects; their exclusion did not significantly change results.

all child health other than via CD4 cell numbers. The opportunistic conditions suffered by the children in this study included *candida albicans*⁷, other fungal infections¹, recurrent otitis media⁵, other bacterial infections², lymphoid interstitial pneumonitis with reactive airway disease⁴, disseminated herpes zoster¹, *Pneumocystis carinii* pneumonia¹, and viral hepatitis¹. Eight were being treated with intravenous gamma globulin (IVIG), two were enrolled in blind clinical trials for IVIG, and 3 were on AZT. Eleven children were developmentally delayed.

Procedure

Data were collected during interviews with the primary caregivers, who were introduced to the experimenter by health care providers at the hospital where the children received treatment. All of the caregivers approached agreed to participate in the study. Questionnaires were administered in interview format because it was believed that the literacy levels of some of the subjects might be inadequate to enable them to complete the measures accurately. Interviews were always scheduled as close in time as possible to the child's immunologic assessment. The average interval between the two was 13 days; it was the same day for 12 subjects, and it never exceeded 2 months.

Measures

Following a brief interview to obtain medical and family history, the following measures were administered:

Child temperament. Child temperament was assessed via parent report with the Revised Infant Temperament Questionnaire^{22,23}. This measure is available for children in four age ranges: birth to one year, one year to three years, three to seven years, and seven to twelve years. The questionnaire yields nine subscales: Activity, Rhythmicity, Approach, Adaptability, Intensity, Mood, Persistence, Distractability, and Threshold. Responses are given in terms of frequencies of infant behaviors. Higher scores reflect more "difficult" or emotional temperaments. To test the study hypotheses regarding child temperament, two temperament factors were created *a priori*. One, a "proneness-to-distress" or "negative" temperament, was formed by combining the Mood, Adaptability and Approach subscales. This combination has been shown to be associated with enhanced adrenocortical activity¹⁹. The other, a "reactive" temperament profile, was created by combining the Intensity and Threshold subscales. These variables have been shown to be related to autonomic nervous system activity^{18,24}. This latter temperament factor concerns both positive and negative emotional reactions and was thus not hypothesized to be related to caregiver distress. The two subscales were not correlated with each other $r(31) = .16$, ns.

Immune Measures

Lymphocyte subset enumeration. The relative numbers of various lymphocyte subsets were quantified by one-and two-color immunofluorescence after staining with monoclonal antibodies and flow cytometry in a computer-linked Ortho System 50 Cytofluorograph as described earlier^{25,26}. Absolute counts were de-

terminated from white blood cell and differential counts. Helper-induced T lymphocytes were estimated by antibodies to the CD4 marker, suppressor/cytotoxic T cells by antibodies to the CD8 antigen, and natural killer (NK) cells by the Leu 11a (CD56) antibody.

Lymphocyte response to PHA. Peripheral blood mononuclear cells were prepared from heparinized blood by the standard Ficoll-Hypaque gradient, and phytohemagglutinin stimulation was determined in triplicate with optimal lectin concentrations and 75×10^3 mononuclear cells as described earlier²⁷. The cultures were harvested on the fifth day after an 18-hour pulse with ³H-thymidine and processed using the automatic cell harvester.

Natural killer cell cytotoxicity. Natural killer cell activity of peripheral blood mononuclear cells was assayed with ⁵¹Cr-labeled K562 erythroleukemia cells as targets under condition similar to those described previously²⁸. Labelled target cells (5×10^3) were incubated with varying numbers of effector cells in medium RPMI-1640 supplemented with 10 percent fetal calf serum in a final volume of 200 microliters. Incubation in round-bottomed microtiter was carried out for four hours. The plates were then centrifuged at $500 \times g$ and the radioactivity was determined after lysis of cells with Triton X at a final concentration of 5 percent; spontaneous lysis was determined in target cells incubated in medium alone. The natural killer cytotoxicity was calculated as percent cytotoxicity = $100 \times ([\text{counts per minute with effector cells}] - [\text{counts per minute in medium alone}]) / (\text{counts per minute released by Triton lysis})$.

Due to hospital and laboratory error, NK cell cytotoxicity was not available for 9 of the children, PHA response was not available for 10, and NK cell numbers were not available for 8.

Results

Means and standard deviations for each of the measures are presented in Table 1.

Table 1. Means and standard deviations for study variables.

Variable	Mean	SD
Temperament subscales		
Negative temperament	9.3	1.9
Reactive temperament	8.2	1.3
Lymphocyte numbers (cells/mm ⁻³)		
# CD4 cells	640	637
# CD8 cells	1003	792
# NK cells	374	493
PHA response (counts/minute)	33003	22123
NK cell activity (percent lysis)	35	22

Table 2. Partial correlations between child temperament and child immune function, controlling for age.

Immune variable	df	Temperament factor	
		Negative	Reactive
# CD4 cells	28	.37*	.49**
# CD8 cells	28	.31*	.14
# NK cells	20	.35*	.13
PHA response	18	-.01	.46*
NK cytotoxicity	19	-.18	-.37*

* $p < .05$ ** $p < .01$ All tests were two-tailed.*Temperament Correlates of Child Immune Function*

Correlations were performed between the two temperament factors and the immune measures. Because child age was significantly correlated with negative temperament, $r(29) = -.31, p < .05$, as well as with NK cell activity, $r(19) = -.38, p < .05$, partial correlations, controlling for child age, were performed. The results are presented in Table 2. Six of the ten correlations performed were significant. Higher numbers of CD4 cells were found in connection with more negative temperament and with more reactive temperament. More negative temperament was also associated with greater numbers of natural killer cells. More reactive temperament was significantly correlated with both of the functional immune measures; the association with NK cell activity was negative, while that with PHA response was positive. The response to PHA is largely T-cell mediated, although the correlation between CD4 numbers and PHA response was not significant $r(18) = .28, p = .12$. In order to test the hypothesis that the result for PHA was mediated by CD4 numbers, which reflect disease status, a partial correlation was performed in which CD4 numbers were controlled. In this analysis, the relation between reactive temperament and PHA response remained nearly significant, $r(15) = .35, p = .065$. In addition, a significant positive association between CD8 cell numbers and negative temperament, and a significant negative association between reactive temperament and NK cytotoxicity, were obtained.

Discussion

Analysis of psychoimmunologic relationships in the children revealed significant associations between temperament and quantitative immune function. Both negative and reactive temperament were associated with greater numbers of CD4 cells. While it is possible that greater emotionality confers a protective effect against T-cell destruction in the progression of HIV infection, another interpretation should be considered. It is possible that CD4 numbers reflect the degree of disease progression, and that more advanced disease is associated with a greater level of viral CNS involvement. Since estimates of the prevalence of

CNS symptomatology in pediatric HIV infection are as high as 90%²⁹, we can assume that many of our subjects had at least some dementia. Adult AIDS dementia is characterized in part by a dampening of affect³⁰, and if this is also true in children, the present finding may be understood as a manifestation of CNS involvement in those with more advanced disease.

More reactive temperament was associated with enhanced lymphocyte response to the mitogen PHA. Since response to PHA is largely T-cell mediated, it was thought that this result may simply accompany that involving T-cell numbers; however, the partial correlation between temperament and PHA response in which CD4 numbers was controlled was marginally significant. This suggests that the result may reflect an influence of temperament on immune function. Interestingly, a recent investigation has demonstrated enhanced mitogen response in depressed children relative to normals¹⁵.

Finally, NK activity was reduced in children with more reactive temperament. NK cells defend against viral infection and cancer, both of which can be features of HIV-spectrum disease. This result contrasts with a recent finding of enhanced NK activity in more autonomically reactive adults with AIDS¹³, pointing to the need for further research in subjects at different developmental levels.

The findings of this preliminary study suggest that temperamental factors may influence and be influenced by the immunologic/disease status of the child. These findings must be regarded as tentative and interpreted with caution; however, their potential importance to our understanding of psychoneuroimmunologic phenomena is great. Furthermore, it is possible that such psychosocial effects on children's immunity generalize beyond the HIV-infected population. Given the extreme paucity of information available regarding psychoimmunologic effects in children generally, and in HIV infection specifically, the potential implications of these relationships merit continued investigation.

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