HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Brain Behav Immun. 2018 October ; 73: 546–549. doi:10.1016/j.bbi.2018.06.019.

Associations between chronic caregiving stress and T cell markers implicated in immunosenescence

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Abstract

Chronic psychological stress is associated with accelerated biological aging, immune dysfunction, and premature morbidity and mortality. Changes in the relative proportions of T cell subpopulations are thought to be a characteristic of immunological aging; however, understanding of whether these changes are associated with chronic psychological stress is incomplete. This study investigated associations between chronic caregiving stress and distributions of T cell phenotypes in a sample of high stress mothers of children with Autism Spectrum Disorder (caregivers; n=91) and low stress mothers of neurotypical children (controls; n=88). Immune markers assessed were naïve (CD45RA+CD62L+), central memory (CD45RA-CD62L+), and effector memory (CD45RA-CD62L-) CD4+ and CD8+ T cells. We also examined the ratio of effector to naïve (E:N) CD4+ and CD8+ T cells. In models adjusted for age, body mass index, race/ethnicity, and antidepressant use, caregivers displayed higher percentages of effector memory CD8+ and CD4+ T cells as well as lower percentages of naïve CD8+ T cells and central memory CD8+ and CD4+ T cells compared to controls. Caregivers also displayed significantly higher E:N ratios for both CD4+ and CD8+ T cells. These findings were also independent of cytomegalovirus infection status. Furthermore, higher parental stress, across both groups, was related to several immune parameters. These findings provide preliminary evidence that chronic parental caregiving stress is associated with changes in relative proportions of T cell subpopulations that are consistent with accelerated immunological aging.

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Introduction

Adaptive immunity undergoes substantial changes with normal aging. This includes a progressive shift in the cellular composition of the T cell compartment, which is marked by a diminution of naïve T cells and an increase in effector memory T cells, particularly CD8+ cells (Goronzy et al., 2015; Pawelec et al., 2005). This process is largely attributable to the combination of a gradual decline in thymus output, which is the source of the naïve T cell pool, and the cumulative exposure across the life course to foreign pathogens, such as cytomegalovirus (CMV), which leads to an accumulation of memory T cells. The capacity to regulate the production, maintenance, and function of T cells in peripheral blood is critical to maintaining adaptive immunity.

Chronic psychological stress, such as the stress experienced as a caregiver for a child with a neurological disability or a loved one with dementia, is a well-known contributor to immune system dysregulation (Glaser and Kiecolt-Glaser, 2005; Segerstrom and Miller, 2004) and has been implicated in accelerated immune system aging (Gouin et al., 2008). Whether chronic stress contributes to a shift in T cell composition characteristic of immunosenescence remains unclear. In a small study of elderly adults who cared for spouses with dementia, caregivers who provided chronic care had fewer memory T cells (CD8+CD62L-and CD4+CD62L-) compared to caregivers who provided less intensive care (Mills et al., 1999). In contrast, percentages of naïve cytotoxic T cells were significantly lower while percentages of effector memory cytotoxic (CD8+) T cells were significantly higher in a sample of patients with post-traumatic stress disorder (PTSD) compared to non-PTSD participants (Sommershof et al., 2009). More frequent symptoms of PTSD and low socioeconomic status have also been associated with a higher ratio of effector memory to naïve (E:N) CD4+ and CD8+ T cells (Aiello et al., 2016a; Aiello et al., 2016b).

The aim of the current study was to investigate group differences in T cell composition using a model of chronic psychological stress, namely comparing high stress maternal caregivers who care for children with Autism Spectrum Disorder (ASD) to a low stress maternal control group caring for neurotypical children. We hypothesized that caregivers would show significantly fewer naïve CD4+ and CD8+ T cells, a greater number of effector T cells, and higher E:N T cell ratios compared to controls. We also investigated whether psychosocial characteristics, CMV serostatus, and contextual factors (e.g., age of the child) may help clarify any group differences.

Methods

Participants and Procedures

Participants were 183 mothers recruited via schools, parenting publications, social media, mailings and ads through child development centers in the San Francisco Bay Area and direct recruitment at the UCSF Autism Clinic; 179 of the mothers had immunophenotyping data available for analyses. Individuals were eligible to participate if they were non-smokers and between the ages of 20 and 50 years old with at least one child between the ages of 2 and 16 years old. In order for the participant to be characterized as a high stress mothers (caregivers), she had to care for a child diagnosed with ASD and report a score of ≥13 on the

Perceived Stress Scale (PSS) (Cohen et al., 1983). Low stress mothers (controls) were characterized as caring for a neurologically typical child and reporting PSS scores of ≤19. The PSS eligibility criteria were based on prior national norms (Cohen et al., 1983) and the overlap in PSS scores across groups facilitated analyses of a continuous stress measure irrespective of caregiver status. All participants reported being premenopausal and in good general health with no major diseases, including no history of coronary heart disease, endocrine disorders, epilepsy, brain injury, autoimmune conditions, severe asthma or lung disease. Potential participants were ineligible if they had cancer or had undergone chemotherapy or radiation in the past 10 years. Structured Clinical Interviews for Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) for Axis I Disorders (SCID) were carried out during the eligibility period and individuals with current psychiatric conditions, including bipolar disorder, post-traumatic stress disorder, and eating disorders were excluded. Additionally, controls with current major depression were excluded; however, this was not exclusionary in caregivers since it is a common consequence of caregiving. All study participants were free from medications known to affect the immune and endocrine system with the exception of antidepressant medication (in caregivers) and oral contraceptives. Two controls were taking antidepressants for reasons other than depression (premenstrual dysphoric disorder and sleep).

At the initial study visit to the laboratory, participants completed a battery of sociodemographic, psychological, and health behavior questionnaires and underwent a fasting morning blood draw. Body mass index (BMI; kg/m^2) was assessed during this visit. Sociodemographic questions included age, child's age, self-identified race/ethnicity, household income, and highest level of education. Child's age since ASD diagnosis was used as a proxy for duration of caregiving for participants who cared for a child with ASD. Participants were paid $110 at the conclusion of the baseline assessment. This study was approved by the Institutional Review Board at the University of California, San Francisco, and written informed consent was obtained for each study participant.

Measures

Perceived psychological stress was assessed using The Perceived Stress Scale (PSS;(Cohen et al., 1983)), which is a well-validated 10-item self-report measure of stress perception (Cohen and Janicki-Deverts, 2012). *Depressive symptoms* were assessed using the 30-item Inventory of Depressive Symptomatology (IDS; (Rush et al., 1986)). *Parental Stress* was measured using the 28-item Parental Stress Scale (Berry and Jones, 1995), which assesses the positive and negative components of parenthood. *Child's ASD severity* was obtained using the total score from the Child Autism Rating Scale (Schopler et al., 1980), which is a 15-item self-report measure completed by the caregivers in this study.

Immunophenotyping

Whole blood was collected into sodium heparin tubes and maintained at room temperature. Specific leukocyte subtypes were enumerated using flow cytometry (FACSCalibur, Becton Dickinson, San Jose, CA). Cell populations percentages were identified using monoclonal antibody combinations (CD45RA CD62L CD4, and CD45RA CD62L CD8) to identify naïve, memory, and effector CD4 and CD8 T cells (BD Biosciences, San Jose, CA). Whole

blood was incubated with antibody for 20 minutes at room temperature, lysed with BD FACS Lysing Solution (Becton Dickinson, San Jose, CA), washed with PBS, and read on the FACSCalibur flow cytometer with approximately 5,000 events being acquired from each preparation. Antibody isotype controls were used to set negative staining criteria. Data were analyzed using CellQuest Pro software (Becton Dickinson, San Jose, CA). Representative figures reflecting the gating strategy used to acquire these data are displayed in the supplement (Supplemental Figures 1 and 2).

Quantification of Cytomegalovirus (CMV)

Frozen serum samples were shipped on dry ice to the HIV/STD Laboratory Core at the University of North Carolina, Chapel Hill. Samples were tested for the presence and quantity of serum IgG antibodies to CMV using the commercially available LIAISON® CMV IgG (DiaSorin, Stillwater, MN), which is an indirect chemilumninescent immunoassay, and analyzed using the LIAISON Analyzer. Run in duplicate, the Analyzer calculates CMV IgG antibody concentrations in U/mL and categorizes results as negative, equivocal, or positive. The cutoff for negative versus positive was determined during European clinical trials, and each tested sample was given an “expected” CMV IgG values based on existing clinical and laboratory data. A value of 0.7 U/ml serves as the lower boundary for a positive sample. The intra and inter-assay variability for this assay is below 10%.

Statistical Analyses

All analyses were conducted using SPSS version 24 (SPSS, Chicago, IL). Pearsonmoment product and point biserial correlations, independent t-tests, $\chi 2$-test, and analysis of covariance (ANCOVA) were conducted. Given the age range of our sample (20 to 50 years), chronological age was retained as a covariate in all models. To identify additional covariates, bivariate associations between possible covariates and immune measures were calculated and those variables significantly associated with our immune measures were retained in adjusted models. This strategy conserved power and increased degrees of freedom in multivariate models. To account for multiple testing in our primary analysis, we employed the false discovery rate method (Benjamini and Hochberg, 1995; Glickman et al., 2014); all effects held using this procedure. Effect sizes were calculated using Cohen’s d for between group differences while adjusted R^2 values are provided for regression analyses.

To test whether psychological measures statistically mediated the links between caregiver status and immune measures, we employed the SPSS macro PROCESS (version 3.0, Model 4), which uses bootstrapping approaches to estimate the indirect path of the proposed mediator along with a 95% confidence intervals based on 20,000 resamples of our data with replacement (Preacher and Hayes, 2004). The distributions of immune measures were largely normally distributed, with the exception of E:N T cell ratios which underwent natural log transformation. Null hypotheses were rejected below a P-value of 0.05.

Results

Descriptive Statistics

Sociodemographic and psychosocial characteristics of the study participants stratified by caregiver status (i.e., caregivers, n=91 and controls, n=88) are presented in Table 1. Caregivers reported higher levels of perceived stress, depressive symptoms, and parental stress than controls. They were also more likely to report current use of antidepressant medication and a lower household income. In contrast, there were no significant group differences in chronological age, age of child, body mass index, racial composition, or education level.

Table S1 includes the correlations between sample characteristics and immune outcomes. In this regard, higher BMI scores were associated with lower percentages of CD4+ and CD8+ effector memory cells. Current antidepressant use was associated with lower percentages of CD8+ naïve and central memory T cells and higher percentages of CD8+ effector memory T cells as well as a higher CD8+ E:N ratio compared to those who did not. Race (% Caucasian) was unrelated to immune outcomes with the exception of percentage of CD4+ central memory, which was higher in Caucasians. CMV seropositivity was associated with higher percentage of CD4+ effector memory T cells.

Chronic caregiving stress and T cell maturation subsets

Table 2 displays differences in immune cell outcomes between caregivers and controls, adjusted for age, BMI, antidepressant use, and race (% Caucasian). Caregivers showed statistically significantly higher percentages of CD4+ and CD8+ effector memory cells as well as lower percentages of CD8+ and CD4+ central memory cells and CD8+ naïve cells compared to controls. Further, caregivers showed higher CD4+ E:N and CD8+ E:N ratios. When CMV serostatus was included as an additional covariate, the findings remained largely unchanged (Table 2), which indicates that CMV infection played a limited role in the observed group differences.

In an effort to identify which characteristics of being a caregiver were associated with T cell maturation profiles, we explored associations between several psychological measures of interest (i.e., perceived stress, depressive symptoms, parental stress), all of which differed between caregivers and controls, and our immune outcomes. As seen in Table S1, higher levels of parental stress were significantly associated with a higher percentage of CD4+ and CD8+ effector memory T cells, a lower percentage of CD8+ naïve T cells and higher CD4+ E:N and CD8+ E:N ratios. Regression analyses revealed that higher parental stress remained significantly associated with higher CD4+ effector memory T cells ($B = 0.10$, $SE = 0.05$, $p = 0.03$) after statistically adjusting for age, BMI, antidepressant use, and race (% Caucasian). Associations between parental stress and the other immune outcomes were no longer significant after covariate adjustment. Next, we tested the possibility that parental stress mediated the associations between caregiver status and percentage of CD4+ effector T cells. In this regard, inclusion of parental stress into the model reduced the effect of caregiver status on CD4+ effector by 18.7%; however, the test of the indirect path was not statistically significant (indirect path: B=0.47, SE=0.54 (95% CI −0.56,1.59).

Discussion

The present findings demonstrate that high stress mothers of children with Autism Spectrum Disorder display higher percentages of effector memory CD8+ and CD4+ T cells, lower percentages of CD4+ and CD8+ central memory T cells, and lower CD8+ naïve T cells as well as an increased ratio of effector to naïve T cells in both CD8+ and CD4+ T cell subsets relative to low stress mothers of neurotypical children. These differences were independent of age, BMI, race (% Caucasian), and antidepressant use as well as positive CMV serostatus- a latent virus well-recognized to contribute to accelerated T cell maturation profiles (Pawelec et al., 2009; Tu and Rao, 2016; Wertheimer et al., 2014).

The present findings fit within a small but growing literature. Sommershof and colleagues (2009) found that patients diagnosed with PTSD showed a shift towards greater proportion of effector memory CD8+ T cells compared to non-PTSD participants, with a similar pattern observed in non-PTSD participants who reported trauma exposure. In addition, higher ratios of effector to naïve CD8+ T cells have been observed in those who met symptom criteria for PTSD in their lifetime or past year compared to no history of PTSD in a large community sample (Aiello et al., 2016a). That said, an earlier study observed fewer effector T cells in chronic caregivers of spouses with dementia as compared to caregivers who did not provide constant care (Mills et al., 1999). This early study was composed of elderly adults, which may change that nature of how stress affects T cell composition. Future studies measuring these T cell markers across various age ranges and in the context of different stressors are warranted.

We also found that caregivers displayed lower percentages of CD4+ and CD8+ central memory T cells compared to low stress controls. To our knowledge, this has not been observed previously in the literature. In contrast to circulating effector memory T cells that can traffic to a variety of peripheral compartments and provide immediate effector function, central memory T cells typically reside in tissues, such as the lymph nodes, spleen, and blood, and rapidly proliferate and differentiate to effector T cells when activated by antigen (Sallusto et al., 2004; Tu and Rao, 2016). The implications of the observed differences between caregivers and controls are not clear as they could reflect either a reduction in the number of available central memory T cells or greater sequestration in secondary lymphoid organs in caregivers compared to controls.

Exploration of the potential psychological pathways through which caregiver status confers its effect on T cell composition revealed parental stress, at least in univariate analyses, to be a salient factor. Specifically, higher parental stress was related to several T cell measures, including higher E:N ratios in both CD4+ and CD8+ T cells, and while level of parental stress did not statistically mediate the effects of caregiver status on T cell outcomes, inclusion of parental stress in our models led to a sizable reduction (18.7%) in the differences in percentages of CD4+ effector T cells between our groups. This suggests that the level psychological stress explicitly tied to parenting may serve as an important pathway to investigate in future studies and larger samples may be needed to more precisely estimate psychological mediators.

There are several limitations to this study that are worth noting. First, this study is cross-sectional in nature and cannot be interpreted as causal. Second, this study lacked a measure of T cell function, and while differences in T cell composition may serve as an index of immune cell aging, the incorporation of functional measures in future work will allow for more meaningful inferences. Third, because the caregivers were all mothers of a child with Autism, it is possible that genetic factors associated with having a child with Autism may also contribute to accelerated maturational T cell profiles. Though this cannot be ruled out, the fact that across the entire sample our measure of parental stress was similarly associated a higher CD8+ and CD4+ E:N ratio, decreases the likelihood that the observed group differences were purely due to genetic differences. Finally, our use of a younger study population compared to earlier work (e.g., Mills et al., 1999) is highly novel and represents a key strength of this study. However, it is possible that the younger age of our participants may have buffered some of the impacts of stress on immune function given the likelihood that these individuals were generally healthy and had younger immunological profiles.

Despite these concerns, the present study provides initial evidence that being a high stress mother of a child with Autism and reports of higher parental stress are associated with a pattern of T cell composition indicative of accelerated T cell aging. If replicated, these findings provide yet another pathway through which chronic caregiving stress may influence susceptibility to infectious illness and other immune-related conditions observed at elevated rates among high stress populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: Support for data collection was provided by NIH grants AG030424 (ESE) and HL117727 (ESE). Dr. Prather's contribution was supported by NIH grant HL112961.

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Highlights

- Caregivers display higher percentages of effector memory T cells than controls.
- Caregivers display lower percentages of naive T cells than controls.
- CMV infection status was unrelated to differences proportions of T cells
- Parental stress was associated with higher effector:naïve T cell ratios.

Table 1

Sociodemographic and psychosocial characteristics of the study sample (n=179).

Variable	Caregivers (High stress; n = 91)	Controls (Low stress; n = 88)	p-value
	Mean (SD) or % (n)	Mean (SD) or % (n)	
Age (years)	42.8 (5.7)	42.2 (4.5)	0.45
Race (% Caucasian)	75.8 (69)	76.1 (67)	0.96
Education (% college and greater)	80.2 (73)	88.6 (78)	0.12
Household Income per year (%)			0.02
< $100,000	32.2 (29)	13.6 (12)	
$100,000–$149,000	24.4 (22)	29.5 (26)	
$150,000–$199,000	15.6 (14)	26.1 (23)	
≥$200,000	27.8 (25)	30.7 (27)	
Age of child (years)	8.2 (2.8)	7.5 (4.2)	0.23
Body mass index (kg/m^2)	25.9 (5.7)	25.1 (4.7)	0.32
Antidepressant use (%)	12.1 (11)	2.3 (2)	0.01
Years since ASD diagnosis (caregiver duration)	5.1 (2.9)	–	–
Perceived Stress (PSS scores)	21.9 (4.7)	15.8 (4.4)	< 0.001
Depressive Symptoms (IDS scores)	19.3 (8.3)	11.9 (5.9)	< 0.001
Parental Stress scores	47.5 (8.8)	37.1 (7.7)	< 0.001
Child ASD severity (CARS score)	32.9 (8.7)	–	–
CMV status (% seropositive)	51.1 (46)	43.7 (38)	0.32

Table 2

Differences in T cell composition between caregivers (high stress) and controls (low stress). Adjusted means and standard errors are displayed.

	Caregivers (High stress)	Controls (Low stress)	F-value	p-value	Effect size[a]
Adjusted for covariates					
CD4+ cells (%)					
Naïve	17.56(0.86)	19.88(0.87)	3.50	0.063	0.29
Central memory	18.12(0.70)	20.45(0.71)	5.34	0.022	0.35
Effector memory	10.13(0.61)	7.65(0.62)	7.82	0.006	0.43
CD4+ E:N ratio*	7.75(2.54)	0.14(2.57)	9.92	0.002	0.48
CD8+ cells (%)					
Naïve	8.49(0.74)	11.20(0.75)	6.44	0.012	0.39
Central memory	5.31(0.52)	7.26(0.52)	6.92	0.009	0.40
Effector memory	6.20(0.48)	4.65(0.48)	5.06	0.026	0.35
CD8+ E:N ratio*	2.85(0.46)	2.07(0.46)	7.11	0.008	0.41
Adjusted for covariates and CMV serostatus					
CD4+ cells (%)					
Naïve	17.61(0.87)	19.78(0.88)	2.98	0.086	0.26
Central memory	18.06(0.70)	20.63(0.71)	6.43	0.012	0.39
Effector memory	9.95(0.61)	7.81(0.62)	5.96	0.016	0.38
CD4+ E:N ratio*	7.92(2.58)	0.04(2.61)	8.23	0.005	0.44
CD8+ cells (%)					
Naïve	8.53(0.74)	11.15(0.75)	6.00	0.015	0.38
Central memory	5.35(0.52)	7.34(0.53)	7.02	0.009	0.41
Effector memory	6.16(0.48)	4.71(0.49)	4.35	0.038	0.32
CD8+ E:N ratio*	2.77(0.46)	2.13(0.47)	6.07	0.015	0.38

Covariates include age, body mass index, antidepressant use, and race (% Caucasian).

*Raw percentages displayed, data analyzed using a natural log (ln) transformation.

[a]Cohen's d.