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Consistent associations between measures of psychological stress and CMV antibody levels in a large occupational sample

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ABSTRACT

Cytomegalovirus (CMV) is a herpes virus that has been implicated in biological aging and impaired health. Evidence, largely accrued from small-scale studies involving select populations, suggests that stress may promote non-clinical reactivation of this virus. However, absent is evidence from larger studies, which allow better statistical adjustment for confounding and mediating factors, in more representative samples.

The present study involved a large occupational cohort ($N = 887$, mean age = 44, 88% male). Questionnaires assessed psychological (i.e., depression, anxiety, vital exhaustion, SF-12 mental health), demographic, socioeconomic (SES), and lifestyle variables. Plasma samples were analyzed for both the presence and level of CMV-specific IgG antibodies (CMV-IgG), used as markers for infection status and viral reactivation, respectively. Also assessed were potential biological mediators of stress-induced reactivation, such as inflammation (C-reactive protein) and HPA function (awakening and diurnal cortisol). Predictors of CMV infection and CMV-IgG among the infected individuals were analyzed using logistic and linear regression analyses, respectively.

Confirming prior reports, lower SES (education and job status) was positively associated with infection status. Among those infected ($N = 329$), higher CMV-IgG were associated with increased anxiety ($\beta = .14$, $p < .05$), depression ($\beta = .11$, $p = .06$), vital exhaustion ($\beta = .14$, $p < .05$), and decreased SF-12 mental health ($\beta = -.14$, $p < .05$), adjusting for a range of potential confounders. Exploratory analyses showed that these associations were generally stronger in low SES individuals. We found no evidence that elevated inflammation or HPA-function mediated any of the associations.

In the largest study to date, we established associations between CMV-IgG levels and multiple indicators of psychological stress. These results demonstrate the robustness of prior findings, and extend these to a general working population. We propose that stress-induced CMV replication warrants further research as a psychobiological mechanism linking stress, aging and health.

1. Introduction

There is convincing evidence that psychological stress impacts health, with the immune system likely playing an important mediating role (Miller et al., 2009; Segerstrom and Miller, 2004). An elegant *in vivo* paradigm to study the impact of stress on the immune system is the reactivation of latent herpes viruses, such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), or cytomegalovirus (CMV) (Glaser and Kiecolt-Glaser, 1997, 2005). These infections are distinctive because the host is unable to completely eliminate the virus, establishing a life-long competition between the pathogen and the host immune system (Sinclair, 2008). In immune competent

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individuals, the virus mostly remains in a dormant (i.e., low-replicating) state, denoted as latency. However, when immune control is weakened, the virus begins to replicate, which in turn stimulates memory B lymphocytes to increase the output of virus-specific IgG antibody. This increase results in the seemingly paradoxical observation that higher antibody levels reflects poorer immune control of the virus (Glaser and Kiecolt-Glaser, 1994; Kuo et al., 2008; van Zanten et al., 1995).

The current study focused on psychosocial factors related to CMV infection status and CMV-IgG levels (reflecting reactivation of the virus). CMV is a highly prevalent β-herpes virus which asymptomatically infects between 30% and 90% of the population in developed countries (Staras et al., 2006). Prevalence of CMV increases nearly linearly with age (Crough and Khanna, 2009; Staras et al., 2006) and with lower socioeconomic status (SES) (Dowd et al., 2009; Enders et al., 2012; Mustakangas et al., 2000; Simanek et al., 2009). CMV has long been considered harmless to healthy immune competent hosts. More recently, this consensus has been revised on the basis of studies that have associated this virus with increased mortality, especially among older adults (Gkrania-Klotsas et al., 2012; Pawelec et al., 2012; Simanek et al., 2011; Strandberg et al., 2009; Savva et al., 2013). These epidemiological findings are complemented by studies showing correlations between CMV infection and poor health outcomes, such as the development of metabolic and cardiovascular diseases (Cheng et al., 2009; Haarala et al., 2012; Hjelmesaeth et al., 2004; Nabipour et al., 2006), autoimmune disease (Söderberg-Nauclér, 2012; Varani and Landini, 2011) some cancers (Dziurzynski et al., 2012; Michaelis et al., 2009), as well as cognitive decline and poor functional status (Aiello et al., 2006; Gow et al., 2013; Moro-García et al., 2012).

One prominent explanation for these health effects pertains to the possible role of CMV in accelerating aging of the immune system, a process denoted as immunosenescence (Pawelec et al., 2009; Turner et al., 2014). Indeed, studies show that CMV infection and CMV-IgG levels are associated with markers of impaired immunity that characterize aging. These include impaired vaccination responses (McElhaney et al., 2012; Turner et al., 2014), increased inflammation (Freeman, 2009; Qiu et al., 2008), selective accumulation of T-lymphocytes with impaired responsiveness to mitogens (Chidrawar et al., 2009), reduced telomere length (van de Berg et al., 2010), and reduced telomerase activity (Dowd et al., 2013). Together these findings suggest that research identifying factors that predict CMV infection status and reactivation may significantly contribute to understanding the determinants of healthy aging (Nikolich-Zugich, 2008).

Psychological stress has been identified as one of the factors that can drive subclinical CMV replication, representing a potential mechanism linking stress, immunity and aging (Bosch et al., 2012). In one of the earliest studies, Lycke et al. (1974) found that hospital psychiatric patients had higher CMV-IgG than healthy controls. Subsequent confirmations were provided by naturalistic stress studies involving caregiving (Pariante et al., 1997), spaceflight (Mehta et al., 2000), academic exams (Glaser et al., 1985; Matalka et al., 2000; Sarid et al., 2004), post-traumatic stress disorder (PTSD) (Uddin et al., 2010), and childhood adversity (Dowd et al., 2012; Fagundes et al., 2013). Studies assessing self-reported stress confirmed these associations, and helped to further characterize the psychological variables involved. For example, studies in older adults identified depression and anxiety as factors associated with higher CMV-IgG (Phillips et al., 2008; Trzonkowski et al., 2004). In a cohort of cardiovascular patients, Appels et al. (2000a) found higher CMV antibody levels among those reporting vital exhaustion (VE), a state characterized by lack of energy, increased irritability, and feelings of demoralization (Appels et al., 2000b; Appels and Mulder, 1988). Related, higher levels of fatigue were associated with higher CMV-IgG in breast cancer patients (Fagundes et al., 2012).

Despite apparently consistent associations between stress and CMV reactivation, the interpretation of these findings is hampered by some limitations. First, many of the aforementioned studies allowed only limited statistical adjustments due to very small sample sizes.[1] This leaves ambiguity with regard to the proper interpretation of these findings (e.g., potential confounding). A second limitation is that prior reports involved samples drawn from select populations, like patient groups, astronauts, or older adults, which creates uncertainty with regards to the generalizability of the findings. To determine the robustness and generalizability of the observed associations between psychological factors and impaired viral control, research in larger and more representative populations would be needed (Dowd et al., 2008).

A further limitation of the extant literature is that little attention has been paid to possible intermediate mechanisms. For example, experimental studies show that inflammatory mediators (Döcke et al., 1994; Fagundes et al., 2012; Stein et al., 1993) and glucocorticoids (Lathey and Spector, 1991; Tanaka et al., 1984a) can promote CMV reactivation. As these factors may also become elevated in response to psychological stress, these represent indirect pathways linking stress and CMV reactivation (cf. Fagundes et al., 2012). In order to address these limitations, the present study investigated associations between CMV reactivation, anxiety, depression, and vital exhaustion in a large sample of working adults. Analyses involved adjustment for demographic factors and health behaviors, and also tested if inflammation and HPA activity may act as possible mediators. Informed by prior research showing a larger impact of stress in low-SES individuals (Brydon et al., 2004; Gruenewald et al., 2006), we also performed exploratory analyses to determine if associations between psychological predictors and CMV-IgG may vary by SES group.

2. Materials and methods

2.1. Participants

The present study was conducted in a cross-sectional sample of the Mannheim Institute of Public Health Industrial Cohort Studies (MICS), consisting of 887 employees who took part in a voluntary company health check (Herr et al., 2012; Li et al., 2012). Participant characteristics are presented in Table 1. Participants were compensated for lost working hours and received a personalized health report. All data was anonymized before analysis. The study was approved by the Ethical Committee of the Mannheim Medical Faculty, Heidelberg University, and all participants signed informed consent.

2.2. Procedures

Participants arrived in the morning between 06:45 and 08:45 h for assessment. After a fasting blood draw, participants were seated separately in a quiet room to fill out questionnaires at a location away from their usual workplace. Demographic, medical, and health behavior data were assessed by questionnaire, and anthropometric measurements (e.g., height, weight, waist and hip circumference, blood pressure) were determined by trained personnel, using standard procedures.

[1] To date only 4 studies had an $N > 50$, two of which involved cancer patients or survivors Fagundes et al. (2012), Jaremka et al. (2012) two studied older adults Bennett et al. (2012), Phillips et al. (2008).