Cytomegalovirus is associated with depression and anxiety in older adults

Phillips, Anna; Carroll, Douglas; Khan, N; Moss, Paul

DOI:
10.1016/j.bbi.2007.06.012

Document Version
Peer reviewed version

Citation for published version (Harvard):
Phillips, A, Carroll, D, Khan, N & Moss, P 2008, 'Cytomegalovirus is associated with depression and anxiety in older adults', *Brain, Behaviour, and Immunity*, vol. 22, no. 1, pp. 52-55. https://doi.org/10.1016/j.bbi.2007.06.012

Post-print, not final published version. Cite this article as: Phillips, A.C., Carroll, D., Khan, N., & Moss, P. (2008). Cytomegalovirus is associated with depression and anxiety in older adults. *Brain, Behavior and Immunity,* 22, 52-55. http://dx.doi.org/10.1016/j.bbi.2007.06.012

Cytomegalovirus is associated with depression and anxiety in older adults.

Anna C. Phillips[a] PhD, Douglas Carroll[a] PhD, Naeem Khan[b] PhD, and Paul Moss[b] MD PhD

[a]School of Sport and Exercise Sciences, [b]Cancer Studies, School of Medicine
University of Birmingham
UK

Address correspondence to: Anna C. Phillips, School of Sport & Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. Tel: 0044 121 414 4398 Fax: 0044 121 414 4121 E-mail address: A.C.Phillips@bham.ac.uk

Abstract

Infection with cytomegalovirus (CMV), a beta-herpesvirus, is common within the population. Although asymptomatic, infection is associated with increased serum concentrations of cytokines such as TNFα and IL-6, which are also related to mood and wellbeing. The present study examined whether infection with CMV was associated with mood in a community-based sample of older adults. Blood samples and scores on the General Health Questionnaire were available for 137 participants. Serum was analysed for the presence of CMV-specific IgG and the antibody titre was used as an indirect measure of viral load. The majority of the participants (66%) were CMV seropositive and seropositive status was not associated with psychological morbidity. However, within the CMV positive group, individuals with higher CMV-specific antibody titres were more likely to be depressed, anxious, and suffer more overall psychological morbidity. This association could be mediated by the impact of affect-moderating cytokines secreted through the CMV-specific immune response.

Keywords: cytomegalovirus; depression; anxiety; ageing

1. Introduction

Cytomegalovirus (CMV) is an ubiquitous β-herpesvirus with prevalence rates of infection as high as 90% (Akbar and Fletcher, 2005). Infection with CMV is usually asymptomatic although it may be accompanied by clinical symptoms (Stinski, 1991). Immunocompromised individuals, such as those with HIV infection, often display symptomatic CMV infections such as interstitial retinitis or pneumonia (Rasmussen, 1991). CMV infection may also contribute to immunosenescence (Olsson et al., 2000), and thus an increased susceptibility to infectious disease and increased risk of mortality in the very old (Almanzar et al., 2005; Pawelec et al., 2005). CMV is also considered to be associated with increased concentrations of pro-inflammatory cytokines, another marker of immunosenescence (Forsey et al., 2003; Franceschi et al., 1999; Licastro et al., 2005), including TNFά and IL-6 (Trzonkowski et al., 2003), and IFNγ (Almanzar et al., 2005; Khan et al., 2002).

Such cytokines are also related to mood and wellbeing, particularly in the context of infectious or inflammatory illness, and are considered to incite sickness behaviours (e.g. fatigue, somnolence) (Dantzer, 2006; Kelley et al., 2003), depressed mood (Reichenberg et al., 2001; Wright et al., 2005) and anxiety (Maes et al., 1998). There is also considerable interest in the role of pro-inflammatory cytokines in the onset of depression (Anisman and Merali, 2003; Irwin, 2002; Miller and O'Callaghan, 2005). One previous study of individuals with acute Epstein-Barr virus, Ross River virus, or Q fever infection (Vollmer-Conna et al., 2004) has documented an association between levels of IL-1β and IL-6 and sickness behaviours including anhedonia (inability to enjoy activities), impaired concentration, and malaise, which overlap considerably with the symptoms of mild depression. In a recent small scale study, older adults with minor or major depression displayed higher CMV antibody titres than matched controls (Trzonkowski et al., 2004). Similarly, in cardiac patients, those reporting greater depressive symptoms were more likely to be seropositive to CMV (Miller et al., 2005). The present study examined whether infection with CMV was associated with mood and psychological morbidity in a community-based sample of older adults. It was hypothesised that those with higher CMV antibody titres would report more symptoms of depression and anxiety.

2. Method

2.1 Participants

Data were available for 137 older adults (62 men and 75 women), recruited from medical practices in Birmingham, UK. All participants were aged 65 years or older (mean = 73.6, SD = 5.89, range = 65-91 years) and had no history of negative reactions to blood sampling, no acute infection, or known current immune disorder. All but four participants described themselves as

"white"; half (51%) of the sample had held non-manual occupations. The majority (89%) were non-smokers and only 24% admitted drinking one unit or more of alcohol per day; 81% indicated that they for less than eight hours per night on average. Sixty-five percent reported some type of ongoing chronic medical condition (excluding cancer and diabetes), the most common being and hypertension (36%) and rheumatoid arthritis (35%). Seventy-five percent were taking some type of medication (excluding immunosuppressants or enhancers), mainly for high blood pressure (35%), and arthritis (8%). The study was approved by the appropriate Research Ethics Committees.

2.2 Study Design

Elderly patients attending their doctor's surgery for routine annual influenza vaccination were invited to participate. Those who agreed and met the inclusion criteria provided a single venous blood sample before vaccination and took home a questionnaire pack to return by mail.

2.3 Questionnaires

Standard socio-demographic and clinical information (reported above) was obtained by questionnaire. Participants also completed the General Health Questionnaire (GHQ-28) (Goldberg and Williams, 1988) in reference to the past month. This measure is widely used for detecting psychological distress and yields four robust factors with acceptable psychometric properties(Goldberg and Williams, 1988): somatic symptoms; anxiety/insomnia; social dysfunction; and severe depression. The simple Likert-type method of scoring (0-1-2-3) was used. Participants' health behaviours were assessed with reference to the previous year by questionnaire, for full details see (Phillips et al., 2006).

2.4 Blood samples, and virological assays

Venous blood was collected from an ante-cubital vein into a plain 7ml tube (BD Vacutainer, Meylan Cedex). The samples were allowed to clot for at least one hour, were centrifuged at 3500 rpm for 5 min, and the separated serum was frozen at –20 °C until assayed. Serum was analysed for the presence of CMV infection by quantitative determination of CMV-specific IgG antibody titre in duplicate using a standard enzyme immunoassay kit (BioCheck Inc, California) with a sensitivity of 100%, specificity of 97.6%, and accuracy of 99%. The coefficients of inter-assay variation were all <10%. In this test, individuals with a serum IgG titre of $\geq$1.2 IU/ml are considered to be seropositive, indicating prior exposure to the virus.

2.5 Data Reduction and Analysis

As scores on the GHQ-28 and its sub-scales were highly skewed, binary variables (high and low) were created using median splits. Chi-square and logistic regression were used to determine whether CMV status and titres (as separate independent variables) predicted mood and well-being. Where demographic and health behaviour variables were found to be associated with either CMV status/titre or GHQ-28 subscale scores, these variables were entered into the logistic regressions at step one, with the relevant independent variable (CMV serostatus or titre) entered at step two.

3. Results

3.1 CMV and Questionnaire Data

The majority of the participants (66%) were CMV seropositive. Amongst those, the mean CMV-specific antibody titre was 16.4 (4.86) mIU. Participants' mean GHQ-28 score was 15.5 (SD = 7.46), and their mean (SD) scores on each of the subscales were: 3.7 (2.88) for somatic symptoms; 3.8 (3.18) for anxiety; 7.3 (1.92) for social dysfunction; and 0.8 (1.68) for depression.

3.2 Associations between CMV and Mood

CMV seropositive status was not associated with high or low levels of psychological morbidity on the GHQ. However, of those who were CMV seropositive, individuals with higher CMV-specific antibody titres were more likely to report higher depressive symptoms, OR = 1.18 95% CI 1.04 – 1.33, $p = .01$, anxiety, OR = 1.17 95% CI 1.05 – 1.31, $p = .005$, and suffer more overall psychological morbidity, OR = 1.16 95% CI 1.04 – 1.29, $p = .008$. The associations with depression and anxiety are presented in Figure 1.

3.3 Demographic, Clinical, and Health Behaviour Variables

CMV serostatus was not associated with any of the demographic, clinical, or health behaviour variables, although there was a tendency for more participants from manual occupational groups to be CMV seropositive, $\chi^2(1) = 3.23$, $p = .07$. Among the CMV seropositive cohort, none of the demographic, clinical, or health behaviour variables were associated with CMV antibody titre. GHQ scores were not related to any of the demographic, clinical, or health behaviour variables, although there was a tendency for women, $t(135) = 1.83$, $p = .07$, and those taking medication, $t(128) = 1.73$, $p = .09$, to register higher anxiety scores. Entering sex and medication status at step 1 in the logistic regression model failed to attenuate the association between CMV titre and anxiety, OR = 1.21, 95% CI 1.07 – 1.37, $p = .002$, or with depression, OR = 1.18, 95% CI 1.04 – 1.33, $p = .01$. Although there were no significant associations between CMV or GHQ scores and chronic illness status or medication usage, the numbers of participants with inflammatory disorders and taking medication for these illnesses was relatively high. Consequently we created

binary variables for the most common diseases and medications: hypertension, arthritis, anti-hypertensive medication, and arthritis medication. Several logistic regressions were then undertaken, entering these variables at step 1 either separately or together. Neither type of disease or medication attenuated the significant associations observed between CMV-specific antibody titre and depression or anxiety score.

4. Discussion

In this study we observed that the titre of CMV-specific IgG antibody was positively associated with reports of depression and anxiety; individuals exhibiting higher antibody titres against CMV reported more symptoms of depression and anxiety. CMV seropositive individuals as a group were not at an increased risk of negative mood suggesting that infection alone is not the primary risk factor. Higher CMV-specific antibody titres reflect recent or reactivated CMV infection (Musiani et al., 1988) and there is evidence that they are correlated with the CMV antigenemia test which is a quantitative marker for CMV load (van Zanten et al., 1995). In addition the increase in the titre of CMV-specific IgG that is observed in association with ageing is believed the reflect the increased frequency of viral reactivation within this cohort (Stowe et al., 2007; Torfason et al., 1981). The implication of our findings is that it is the magnitude of the CMV-specific immune response, rather than CMV infection itself, that is associated with symptoms of depression and anxiety. The present findings resonate with those of a recent small-scale study of older adults with clinical depression who displayed higher CMV antibody titres, higher levels of serum and *in vitro* stimulated IL-6, and higher stimulated concentrations of TNFά, compared to non-depressed controls (Trzonkowski et al., 2004). Our results appear to contrast somewhat with those of Miller et al. (2005) who reported that seropositivity to CMV in cardiac patients was correlated with level of depressive symptoms irrespective of antibody titre. However, the association between CMV infection and mood may be differently manifest in cardiac patients who have recently experienced an acute coronary syndrome compared to a broader population sample. Further, differences between studies in the criterion for determining the cut-off for seropositivity make direct comparison difficult.

A limitation of the present analysis is the cross-sectional design which limits the ability to assign causality. As higher antibody titres against CMV have been associated with increased concentrations of pro-inflammatory cytokines in clinically depressed older adults (Trzonkowski et al., 2004), it is probable that CMV titre contributes to feelings of anxiety and depression. However, it also remains possible that the relationship between these variables is in the opposite direction. Symptoms of depression and anxiety could induce CMV reactivation, resulting in greater antibody

titres against the virus, given that such effects have been previously attributed to psychological stress (Glaser et al., 1985; Mehta et al., 2000). A prospective longitudinal design would be necessary to discount this possibility. Of course it could also be the case that some third unmeasured factor, such as underlying vascular disease which is related to CMV status (Nieto et al., 1996) and symptoms of depression (Tiemeier et al., 2004), could mediate the association observed here. However, statistical adjustment for hypertension and arthritis failed to attenuate the significant associations observed. Future studies might include multiple assessments of mood and CMV titre in order to better establish the most likely direction of effect and might also examine underlying mechanisms by measuring concentrations of pro-inflammatory cytokines, including TNFά, IL-6, IL-1β, and IFNγ. It would also be interesting to examine the association between CMV and psychological status in older adults already displaying concomitant immunosenescence.

In summary, the present study provides preliminary evidence that the magnitude of the CMV-specific immune response is associated with psychological morbidity in a community sample of older adults. This underscores the powerful link between immunological and psychological function. The consequences of CMV infection for psychological well-being merit further study.

References

Akbar, A.N., Fletcher, J.M., 2005. Memory T cell homeostasis and senescence during aging. Curr Opin Immunol 17, 480-485.

Almanzar, G., Schwaiger, S., Jenewein, B., Keller, M., Herndler-Brandstetter, D., Wurzner, R., Schonitzer, D., Grubeck-Loebenstein, B., 2005. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons. J Virol 79, 3675-3683.

Anisman, H., Merali, Z., 2003. Cytokines, stress and depressive illness: brain-immune interactions. Ann Med 35, 2-11.

Dantzer, R., 2006. Cytokine, sickness behavior, and depression. Neurol Clin 24, 441-460.

Forsey, R.J., Thompson, J.M., Ernerudh, J., Hurst, T.L., Strindhall, J., Johansson, B., Nilsson, B.O., Wikby, A., 2003. Plasma cytokine profiles in elderly humans. Mech Ageing Dev 124, 487-493.

Franceschi, C., Valensin, S., Fagnoni, F., Barbi, C., Bonafe, M., 1999. Biomarkers of immunosenescence within an evolutionary perspective: the challenge of heterogeneity and the role of antigenic load. Exp Gerontol 34, 911-921.

Glaser, R., Kiecolt-Glaser, J.K., Speicher, C.E., Holliday, J.E., 1985. Stress, loneliness, and changes in herpesvirus latency. J Behav Med 8, 249-260.

Goldberg, D., Williams, P., 1988. A user's guide to the General Health Questionnaire. NFER-Nelson, Berkshire.

Irwin, M., 2002. Psychoneuroimmunology of depression: clinical implications. Brain Behav Immun 16, 1-16.

Kelley, K.W., Bluthe, R.M., Dantzer, R., Zhou, J.H., Shen, W.H., Johnson, R.W., Broussard, S.R., 2003. Cytokine-induced sickness behavior. Brain Behav Immun 17 Suppl 1, S112-118.

Khan, N., Shariff, N., Cobbold, M., Bruton, R., Ainsworth, J.A., Sinclair, A.J., Nayak, L., Moss, P.A., 2002. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. J Immunol 169, 1984-1992.

Licastro, F., Candore, G., Lio, D., Porcellini, E., Colonna-Romano, G., Franceschi, C., Caruso, C., 2005. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. Immun Ageing 2, 8.

Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpe, S., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10, 313-318.

Mehta, S.K., Stowe, R.P., Feiveson, A.H., Tyring, S.K., Pierson, D.L., 2000. Reactivation and shedding of cytomegalovirus in astronauts during spaceflight. J Infect Dis 182, 1761-1764.

Miller, D.B., O'Callaghan, J.P., 2005. Depression, cytokines, and glial function. Metabolism 54, 33-38.
Miller, G.E., Freedland, K.E., Duntley, S., Carney, R.M., 2005. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. Am J Cardiol 95, 317-321.
Musiani, M., Zerbini, M., Zauli, D., Cometti, G., La Placa, M., 1988. Impairment of cytomegalovirus and host balance in elderly subjects. J Clin Pathol 41, 722-725.
Nieto, F.J., Adam, E., Sorlie, P., Farzadegan, H., Melnick, J.L., Comstock, G.W., Szklo, M., 1996. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. Circulation 94, 922-927.
Olsson, J., Wikby, A., Johansson, B., Lofgren, S., Nilsson, B.O., Ferguson, F.G., 2000. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. Mech Ageing Dev 121, 187-201.
Pawelec, G., Akbar, A., Caruso, C., Solana, R., Grubeck-Loebenstein, B., Wikby, A., 2005. Human immunosenescence: is it infectious? Immunol Rev 205, 257-268.
Phillips, A.C., Carroll, D., Burns, V.E., Ring, C., Macleod, J., Drayson, M., 2006. Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain, Behav Immun 20, 279-289.
Rasmussen, L.E., 1991. Gene products of cytomegalovirus and their immunologic significance. In: Ho, M. (Ed.), Cytomegalovirus: biology and infection. Plenum Medical Book Company, New York.
Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmacher, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 58, 445-452.
Stinski, M., 1991. Molecular biology of cytomegalovius replication. In: Ho, M. (Ed.), Cytomegalovirus: biology and infection. Plenum Medical Book Company., New York.
Stowe, R.P., Kozlova, E.V., Yetman, D.L., Walling, D.M., Goodwin, J.S., Glaser, R., 2007. Chronic herpesvirus reactivation occurs in aging. Exp Gerontol.
Tiemeier, H., van Dijck, W., Hofman, A., Witteman, J.C., Stijnen, T., Breteler, M.M., 2004. Relationship between atherosclerosis and late-life depression: the Rotterdam Study. Arch Gen Psychiatry 61, 369-376.
Torfason, E.G., Kallander, C., Halonen, P., 1981. Solid-phase radioimmunoassay of serum IgG, IgM, and IgA antibodies to cytomegalovirus. J Med Virol 7, 85-96.

Trzonkowski, P., Mysliwska, J., Godlewska, B., Szmit, E., Lukaszuk, K., Wieckiewicz, J., Brydak, L., Machala, M., Landowski, J., Mysliwski, A., 2004. Immune consequences of the spontaneous pro-inflammatory status in depressed elderly patients. Brain Behav Immun 18, 135-148.
Trzonkowski, P., Mysliwska, J., Szmit, E., Wieckiewicz, J., Lukaszuk, K., Brydak, L.B., Machala, M., Mysliwski, A., 2003. Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination-an impact of immunosenescence. Vaccine 21, 3826-3836.
van Zanten, J., Harmsen, M.C., van der Giessen, M., van der Bij, W., Prop, J., de Leij, L., The, T.H., 1995. Humoral immune response against human cytomegalovirus (HCMV)-specific proteins after HCMV infection in lung transplantation as detected with recombinant and naturally occurring proteins. Clin Diagn Lab Immunol 2, 214-218.
Vollmer-Conna, U., Fazou, C., Cameron, B., Li, H., Brennan, C., Luck, L., Davenport, T., Wakefield, D., Hickie, I., Lloyd, A., 2004. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychol Med 34, 1289-1297.
Wright, C.E., Strike, P.C., Brydon, L., Steptoe, A., 2005. Acute inflammation and negative mood: mediation by cytokine activation. Brain Behav Immun 19, 345-350.

Figure 1: CMV titres for those with low and high depression and anxiety scores