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Cytomegalovirus infection and cognitive abilities in old age

Alan J. Gow [a,b,c,*,1], Charlotte M. Firth [d,1], Rowan Harrison [e], John M. Starr [a,e,f], Paul Moss [d], Ian J. Deary [a,b]

[a] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[b] Department of Psychology, University of Edinburgh, Edinburgh, UK
[c] Department of Psychology, School of Life Sciences, Heriot-Watt University, Edinburgh, UK
[d] School of Cancer Sciences, University of Birmingham, Birmingham, UK
[e] Geriatric Medicine Unit, University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK
[f] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK

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ABSTRACT

Cytomegalovirus infection has been implicated in cognitive impairment in studies using brief clinical assessments though findings are inconsistent. The association between cytomegalovirus infection, measured as serostatus or a semiquantitative assessment of antibody level, and cognitive abilities in a sample of older adults was examined. Cytomegalovirus status was assessed at a mean age of 70 years in 1061 participants of the Lothian Birth Cohort 1936. Cognitive ability scores were available for general cognitive ability, processing speed, memory, and vocabulary. Background demographic and environmental factors included father's social class, years of education, childhood cognitive ability, overcrowding in childhood, and access to indoor toilet facilities. Cytomegalovirus seropositive individuals had lower cognitive ability at age 70: mean IQ was 99.1 (SD, 15.1) versus 102.4 (SD, 13.1) in seronegative individuals ($t = 3.65$; $p < 0.001$). The likelihood of contracting cytomegalovirus infection by age 70 was predicted by a number of demographic and environmental factors and, after accounting for these, cytomegalovirus infection (considered as serostatus) was not cognitively detrimental. Within cytomegalovirus seropositive individuals, however, higher cytomegalovirus antibody levels were associated with lower general cognitive ability.

1. Introduction

Cytomegalovirus (CMV) is a common beta-herpes virus which infects most of the world's population (for example, prevalence rates vary from 45% to 100% in women of reproductive age) (Cannon et al., 2010). CMV is never cleared from the host but establishes a state of chronic infection which can be detected through the presence of CMV-specific antibodies. CMV seroprevalence varies in different populations and depends on a number of environmental factors. The rate of CMV seroprevalence is higher in women and those from lower socioeconomic groups (Bate et al., 2010) and is also more common in older individuals because seroprevalence increases with age (Staras et al., 2006). CMV can reactivate throughout the life course in seropositive individuals and leads to the development of a very strong CMV-specific immune response. There is considerable interest in the potential for CMV infection to contribute to a decline in functional ability (Aiello et al., 2008), with a particular focus on its role in driving immunosenescence (Pawelec et al., 2009).

CMV has been associated with impaired cognition in groups of people with pre-existing clinical conditions, including schizophrenia, Alzheimer's disease, and cardiovascular disease (Blasko et al., 2007; Shirts et al., 2008; Strandberg et al., 2003). The few studies that examined whether CMV predicts cognitive outcomes in otherwise healthy older people reported inconsistent results (Aiello et al., 2006; Mathei et al., 2011). Aiello et al. (2006) suggested that higher CMV antibody level predicted 4-year cognitive decline assessed by a modified Mini Mental State Examination (MMSE) and concluded that "CMV [was] an important marker of cognitive decline in older people, even after controlling for major risk factors." However, the detailed results presented by CMV antibody level quartiles are not strongly supportive of this conclusion. Mathei et al. (2011) reported no association between CMV and MMSE, although they suggested this might be explained by the mean age of the cohort, who were all older than 80 years when assessed.

Previous studies of the potential association of CMV infection with cognition have relied on the MMSE (Folstein et al., 1975), or modified versions of this, to assess cognitive function. This brief test, though a useful screening tool for potential cognitive impairment, displays marked ceiling effects in generally healthy older

* Corresponding author at: Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK. Tel.: +44 131 651 1685; fax: +44 131 651 1771.
E-mail address: A.J.Gow@hw.ac.uk (A.J. Gow).
[1] These authors contributed equally to the report.

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samples and is strongly influenced by previous intelligence (Starr et al., 1992). With cognitive ability as an outcome, the stability of cognitive function across time must also be considered. For example, inflammatory processes have been implicated in cognitive decline; however, associations between inflammation and cognitive function in old age were removed when a measure of cognitive ability from youth was available (Luciano et al., 2009b). The current study therefore used a comprehensive battery of cognitive ability tests across the domains of general cognitive ability, processing speed, and memory, to examine the effect of CMV infection on cognitive ability in old age, in the presence of various potential life course confounders of an effect.

2. Methods

2.1. Participants

Participants were the 1091 members of the Lothian Birth Cohort 1936 (LBC1936), a prospective longitudinal study of cognitive aging. Full recruitment details have been provided (Deary et al., 2007, 2012). Briefly, participants were all born in 1936 and most completed a test of mental ability when aged 11 in the Scottish Mental Survey of 1947 (SMS1947) (Scottish Council for Research in Education, 1949). Surviving participants of the SMS1947 residents in Edinburgh and the Lothians were recruited into the LBC1936 between 2004 and 2007 at a mean age of 70 years. The mean follow-up interval was 58.6 years (SD, 0.8), ranging from 56.6 to 59.9 years. Participants completed detailed cognitive, medical, and physical tests, provided background demographic and lifestyle information, and provided blood samples for biochemical, hematological, and genetic analyses (Deary et al., 2007).

2.2. CMV assessment

CMV was assessed in plasma samples collected at age 70 years, using a CMV enzyme-linked immunosorbent assay (ELISA). Mock and viral-infected lysate was coated onto ELISA plates and incubated overnight. Plasma samples (1:600 dilution) and appropriate standards (a mixture of 3 CMV-positive plasma samples) were added to the plates for 1 hour. The plate was washed 3 times. An anti-human IgG-HRP (horseradish peroxidase) secondary antibody was then added to the plate for 1 hour. After washing, TMB (3, 3′, 5, 5′-tetramethylbenzidine) substrate was added and the plate kept in the dark for 10 minutes before addition of 1 M HCl. The sample was assessed using an ELISA reader at 450 nm. To determine CMV titres, mock values were first subtracted from lysate values. The data were then analyzed using GraphPad Prism Version 5.03 (GraphPad Software, San Diego, CA, USA), and CMV titres were calculated with reference to the standard curve. Values greater than 10 were considered to be seropositive. To ensure accuracy, all samples were tested in duplicate. CMV data were available for 1061 participants.

2.3. Cognitive ability

At age 70 years, participants completed a battery of standardized cognitive tests from the Wechsler Adult Intelligence Scale-III UK (Wechsler, 1998a) and the Wechsler Memory Scale-III UK (Wechsler, 1998b), supplemented by the processing speed tests of reaction time (Cox et al., 1993) and inspection time (Deary et al., 2004). These have been described in detail elsewhere (Deary et al., 2007). Summary factor scores from Principal Components Analysis were calculated for general cognitive ability, processing speed, and memory (Corley et al., 2010; Luciano et al., 2009a). Participants also completed the National Adult Reading Test (NART) (Nelson and Willison, 1991), often used as an indicator of maximal previous cognitive ability. Finally, participants completed the Moray House Test (MHT) (Scottish Council for Research in Education, 1933), an omnibus test of intelligence which they had previously completed at age 11 years in the SMS1947 (Scottish Council for Research in Education, 1949). MHT scores were corrected for age in days and converted to an IQ-type scale (mean = 100, SD = 15), referred to as age-70 IQ throughout.

2.4. Covariates

A number of covariates which are risk factors for CMV infection or predictors of cognitive ability in later life were considered. At the age 70 assessment, participants were asked to provide background demographic and environmental information about their childhood, specifically for when they were aged approximately 11 years. Participants reported the number of people they lived with and the number of rooms in the house, used to calculate an overcrowding index (people per room; high outliers were trimmed). Participants also reported: whether their household had indoor or outdoor toilet facilities; their father's occupation to allow father's social class to be coded (categorized from I, professional, to V, unskilled) (General Register Office, 1956); and the number of years they spent in full-time, formal education. Participants' scores on the MHT at age 11 years were available and were transformed into an age-corrected, IQ-type score, as in Section 2.3 (referred to as age-11 IQ).

Participants were asked to report their highest status occupation, which was used to assign a social class coding (Office of Population Censuses and Surveys, 1980). This was also coded I, professional, to V, unskilled, with class III split into nonmanual and manual groups. Married women also reported their husband's occupation, and were assigned the higher social class. A medical history was collected, including the presence and/or absence of the following conditions: hypertension, diabetes, and cardiovascular disease (CVD). C-reactive protein (CRP), a marker of inflammation, was assessed from blood samples; values less than the lower sensitivity of the assay (<3.0 mg/L) were recorded as 1.5 mg/L (Luciano et al., 2009b). Participants completed the MMSE (Folstein et al., 1975), which was used for descriptive purposes only, not as an outcome measure of cognitive ability.

2.5. Statistical analyses

All statistical analyses were performed using IBM SPSS Version 19 (SPSS Inc, Chicago, IL, USA). Comparisons were made between CMV seropositive and seronegative individuals using the *t* test for continuous covariates or χ^2 for binary covariates. Predictors of CMV serostatus were examined by logistic regression, with background factors included as independent variables. General linear models were then run to examine associations between CMV serostatus and cognitive ability in the presence of relevant covariates. In the first model, age and sex were included. Partial eta^2 values are reported as a measure of the effect size. Each subsequent model included a single covariate to examine changes in the CMV–cognition association. Attenuation of the effect, indicated by a reduction in the partial eta^2, suggests confounding by the covariate or that the covariate is a potential mediator of the association.

For seropositive individuals, the continuous CMV antibody level data were also used. Data were first log-log transformed to a normal distribution and the general linear models were repeated using this transformed CMV variable.

3. Results

Descriptive data for the 1061 participants with CMV data are presented (Table 1). The sample was balanced in terms of sex and