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Full-length Article

Association of cytomegalovirus and Epstein-Barr virus with cognitive functioning and risk of dementia in the general population: 11-year follow-up study

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ABSTRACT

Background: Earlier studies have documented an association between cytomegalovirus and cognitive impairment, but results have been inconsistent. Few studies have investigated the association of cytomegalovirus and Epstein-Barr virus with cognitive decline longitudinally. Our aim was to examine whether cytomegalovirus and Epstein-Barr virus are associated with cognitive decline in adults.
Method: The study sample is from the Finnish Health 2000 Survey (BRIF8901, $n = 7112$), which is representative of the Finnish adult population. The sample was followed up after 11 years in the Health 2011 Survey. In addition, persons with dementia were identified from healthcare registers.
Results: In the Finnish population aged 30 and over, the seroprevalence of cytomegalovirus was estimated to be 84% and the seroprevalence of Epstein-Barr virus 98%. Seropositivity of the viruses and antibody levels were mostly not associated with cognitive performance. In the middle-aged adult group, cytomegalovirus serointensity was associated with impaired performance in verbal learning. However, the association disappeared when corrected for multiple testing. No interactions between infection and time or between the two infections were significant when corrected for multiple testing. Seropositivity did not predict dementia diagnosis.
Conclusions: The results suggest that adult levels of antibodies to cytomegalovirus and Epstein-Barr virus may not be associated with a significant decline in cognitive function or with dementia at population level.

1. Introduction

Human cytomegalovirus (CMV, also known as human herpesvirus-5, HHV-5) and Epstein-Barr virus (EBV) are among the most common viruses in humans. Both viruses are members of the herpesvirus family and form a lifelong latent infection. CMV and EBV spread mostly through bodily fluids, such as saliva. Primary infections, as well as subsequent virus reactivations, are often asymptomatic or cause only mild symptoms, and therefore most people do not know that they have been infected. However, primary infection or reactivation of the viruses can be potentially life-threatening to immunocompromised persons (Emery, 2001; Hodson et al., 2005). In addition, primary infection of CMV during pregnancy may cause cognitive impairment, hearing loss or visual impairment to the unborn baby (Dollard et al., 2007). In Finland, the seroprevalence of CMV was 56% in pregnant women in South-Western Finland (Alanen et al., 2005), and in another study the seroprevalence in pregnant women was 76% in a low socioeconomic area and 61% in a high socioeconomic area of Helsinki (Mustakangas et al., 2000). The seroprevalence of EBV has been estimated to be over 90% (Cohen, 2000; Puhakka et al., 2016). Infections are slightly more prevalent in women and in persons with low socioeconomic status (Cannon et al., 2010; Dowd et al., 2013).

Two longitudinal studies with approximately 1000 elderly participants found an association between CMV and cognitive decline.

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Barnes et al. noticed an association between CMV seropositivity and cognitive decline and risk of Alzheimer's disease (Barnes et al., 2015). Another study detected an association between CMV immunoglobulin G (IgG) antibody level (serointensity) and cognitive decline (Aiello et al., 2006). Gow et al. concluded that CMV infection per se may not associate with cognitive ability when controlling for background factors associated with the risk of CMV infection, but having a high level of CMV antibodies associated with a lower level of cognitive ability (Gow et al., 2013). In contrast, Tarter et al. did not find an association between CMV seropositivity and cognitive impairment in a group of 5000 persons over 60 years of age (Tarter et al., 2014).

In non-elderly adults, the association between CMV and cognitive functioning has been studied in few cross-sectional studies with a large sample size. Tarter et al. with almost 5000 middle-aged persons, detected an association between CMV seropositivity and cognitive impairment in two out of four cognitive variables (Tarter et al., 2014). Dickerson et al. reported an association between high CMV antibody levels and cognitive functioning in 512 individuals (Dickerson et al., 2014).

The effect of CMV infection on cognitive functioning is expected to be small (Gow et al., 2013; Tarter et al., 2014) and therefore addressing the question requires a large sample size. Previously only a few studies have had adequate sample sizes for investigating the association between CMV and cognitive functioning (Aiello et al., 2006; Barnes et al., 2015; Tarter et al., 2014). In addition, because the risk for CMV infection is associated with many background variables that are also associated with cognitive functioning, the detected association between CMV infection and cognitive functioning could result from not being able to perfectly control for background factors (i.e. residual confounding) (Gow et al., 2013). This issue can be solved by using longitudinal data. Although some longitudinal studies have been published in the elderly (Aiello et al., 2006; Barnes et al., 2015), as far as we know, no longitudinal studies on the effects of CMV infection on cognitive functioning in a non-elderly adult population have been published.

EBV has been less studied than CMV in terms of association with cognitive functioning. Dickerson et al. studied the association between EBV and cognition in two studies: 521 non-elderly persons and 229 persons with schizophrenia, and did not detect any association (Dickerson et al., 2014, 2003). Also in a study with 1000 adolescents, EBV was not associated with cognitive performance (Jonker et al., 2014). However, a meta-analysis with only three small samples found an association between EBV and Alzheimer's disease (Steel and Eslick, 2015).

The purpose of the present study was to examine whether CMV and EBV seropositivity and antibody levels are associated with cognitive decline in adults and the elderly and with dementia diagnosis using a large, representative population sample.

2. Methods

2.1. Participants

This study is based on the Finnish Health 2000 Survey (BRIF8901), which is a representative, two-stage stratified cluster sample of the Finnish population (Aromaa and Koskinen, 2004). The sample comprised 8028 persons aged 30 years or over living in mainland Finland. Finland was divided into 20 strata based on the five university hospital regions and the 15 largest cities in Finland. From each university hospital region, 16 healthcare districts, including the largest cities, were chosen as clusters. The ultimate sampling units were persons who were selected by systematic random sampling from the healthcare districts. People who were 80 years or older were oversampled using double inclusion probability. The study protocol was approved by the Ethics Committee of the National Public Health Institute and the Hospital District of Helsinki and Uusimaa (HUS) (Heistaro, 2008). Written informed consent was obtained.

Of the total sample, 7112 (88.6%) participated in the health interview and/or health examination. Data were collected between September 2000 and June 2001, including a home interview and a health examination at the local health centre, or for non-respondents, a condensed interview and health examination performed at home. We excluded persons whose native language was other than Finnish, or was unknown (n = 558), from the analyses of cognitive performance. After the exclusion, the study group comprised 6554 persons.

The Health 2000 sample was followed up in 2011 with the Health 2011 Survey. All persons from the Health 2000 sample who were alive, living in Finland and had not refused to participate in any future studies were invited (n = 5733: 5309 persons whose native language was Finnish), and 4620 participated in the Health 2011 Survey (Markkula et al., 2016).

2.2. Cognitive assessment

The cognitive variables of the present study can be seen in Table 1. Two tests from the CERAD battery (Moms et al., 1989; Pulliainen et al., 1999) were performed by all participants. For the assessment of **verbal fluency**, participants were requested to name as many animals as they could within one minute. The number of correct words was recorded.

In the assessment of **verbal learning and memory**, the participants were shown 10 words one at a time, and were asked to read the words aloud and memorize them. The total number of correctly recalled words was recorded. The words were shown in total three times, each time in a different order. In Health 2000, if the person remembered all the words they were not shown again, and the unshown words were scored as if the person had remembered them. In this study, we used the total number of immediately recalled words after each of the showings as a measure of verbal learning. Short delayed recall after five minutes was categorized for persons who remembered at least 90%, at least 75% (slightly impaired) and <75% (impaired) (Hänninen et al., 2013) of the number of words from the recall in the third showing.

Simple and choice **reaction and movement time** was recorded by Good Response (Metitur oy, Jyväskylä) (Era et al., 1986). The task was to move the index finger when a light lit up from the waiting switch to the switch that turned the light off as fast as possible. In the simple task, the light lit up in the same place at random intervals. In the choice task, the light lit up in different places in the testing panel. The tasks were repeated 12 times. The response was accepted if the response was given within programmed time limits and was within two standard deviations from the mean of the subject. Mean simple reaction and movement

Table 1
Assessed cognitive variables in two age groups in the baseline and in the 11 year follow-up.

	Middle-aged adults		Elderly	
Cognitive variables	Baseline	Follow-up	Baseline	Follow-up
Verbal fluency	×	×	×	×
Verbal learning	×	×	×	×
Verbal short delay recall	×	×	×	×
Simple movement time	×		×	
Simple reaction time	×		×	
Choice movement time	×		×	
Choice reaction time	×		×	
Abbreviated Mini-Mental State Examination (MMSE)			×	×

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