Cytomegalovirus and cardiovascular disease in the oldest old

Cross-sectional analysis of the BELFRAIL cohort

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Abstract

Background: Recent studies have suggested cytomegalovirus (CMV) to be associated with increased risk of cardiovascular disease and mortality in adults. However, evidence supporting this relationship among a very old population is lacking. This cross-sectional study was performed to investigate the association between CMV and cardiovascular disease (CVD) in the oldest old.

Methods: The BELFRAIL study is a observational, population-based cohort study of 567 Belgian subjects aged 80 years and older. Medical history provided by the GP and serological data from 548 subjects were analysed. Logistic regression was used to estimate odds ratios and 95% confidence intervals for various cardiovascular morbidities and the number of CVD by CMV serostatus and anti-CMV IgG antibody titres.

Results: CMV seropositivity was not associated with history of any individual CVD or the number of cardiovascular diseases. Among CMV-seropositives, an anti-CMV IgG antibody titre ≥250IU/mL was significantly associated with a higher number of cardiovascular diseases (OR 1.81, 95%CI 1.21-2.72) and history of decompensated heart failure (OR 2.52, 95% CI: 1.32 - 4.79) after adjustment for confouders.

Conclusions: A high anti-CMV IgG antibody titre, but not seropositivity itself, was associated with a higher number of cardiovascular diseases. In our population of oldest old, the level of anti-CMV IgG antibodies seems to hold a stronger association with adverse outcomes than CMV serostatus itself, possibly implicating the role of disease reactivation.

Achtergrond: Recente studies suggereren dat cytomegalovirus geassocieerd is met een verhoogd risico op cardiovasculaire aandoeningen en mortaliteit bij volwassenen. Bewijs voor deze relatie in een zeer oude populatie ontbreekt echter. Deze cross-sectionele studie werd uitgevoerd om de associatie tussen CMV en cardiovasculaire aandoeningen te onderzoeken in een populatie van oudste ouderen.

Methode: De BELFRAIL studie is een observationele, populatie-gebaseerde cohortstudie van 567 Belgische personen van minstens 80 jaar oud. Medische voorgeschiedenis, verstrekt door de huisarts, en serologische data van 548 patiënten werd geanalyseerd. Via logistische regressie werden odds ratios (OR) en 95% betrouwbaarheidsintervals geschat voor het verband tussen verscheidene cardiovasculaire aandoeningen en het aantal cardiovasculaire ziekten enerzijds, en CMV serostatus en anti-CMV IgG antistoftiters anderzijds.

Resultaten: CMV seropositiviteit was niet geassocieerd met voorgeschiedenis van een bepaalde cardiovasculaire aandoening of het aantal cardiovasculaire aandoeningen. Binnen de CMV-seropositieve groep was een anti-CMV IgG antistoftiter ≥250IU/mL significant geassocieerd met een hoger aantal cardiovasculaire aandoeningen (OR 1.81, 95%CI 1.21-2.72) en een voorgeschiedenis van gedecompenseerd hartfalen (OR 2.52, 95% CI: 1.32 - 4.79), na correctie voor vertekenende factoren.

Conclusie: Een hoge anti-CMV IgG antistoftiter, maar niet CMV-seropositiviteit zelf, was geassocieerd met een hoger aantal cardiovasculaire aandoeningen. In onze populatie van oudste ouderen lijken anti-CMV IgG antistoffen een sterker verband te hebben met een negatieve uitkomst dan CMV serostatus zelf, wat mogelijks kan wijzen op het belang van ziekte-reactivatie in het proces.

Introduction

Human cytomegalovirus (CMV) is DNA virus belonging to the herpes family. CMV infection has a high prevalence in developed countries, ranging from 30% to 90%, with seroprevalence increasing with age [1]. After primary infection the virus establishes a lifelong latency in the host and can reactivate in response to immunosuppression, inflammation, infection or stress[1].
Whereas in healthy subjects, CMV primary infection generally remains asymptomatic or causes a nonspecific febrile illness, in neonates or immunocompromised patients it can cause serious, even life-threatening complications [2]. The morbidity and mortality caused by CMV infection in, amongst others, transplant recipients and HIV-positive subjects has long been established. More recently, increasing attention is being given to the potential clinical importance of CMV seropositivity in the older general population.
Various chronic conditions, such as altered cellular and humoral immunity, frailty endothelial dysfunction, cancer and atherosclerosis have been linked to CMV[3]. Multiple theories concerning the pathways through which CMV influences these conditions exist. The specific mechanisms are not yet fully understood, but are likely to have an immune and inflammatory component. CMV has been shown to cause an increase in CRP and pro-inflammatory cytokines, most notably Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [4]. This increase is most likely the result of disease reactivation or chronic disease activity (through loss of cell-mediated control)[1]. These inflammatory markers have in their turn been shown to be independently associated with all-cause mortality and cardiovascular disease (CVD)[5,6].
Additionally, more direct pathways between CMV and CVD have been examined. CMV antigen and DNA have been identified in atherosclerotic lesions, both cardiac and peripheral[7,8]. CMV presence in the vessel wall is thought to induce smooth-muscle cell proliferation, increased LDL-uptake, expression of cytokines and increase in procoagulant activity by endothelial cells[4].
Clinically, CMV seropositivity has been linked to increased risk of frailty [9–11], cardiovascular disease [12–14], all-cause mortality [4,9,10,15] and cardiovascular mortality [4,12,14–19].
Several large studies reported CMV serostatus and/or anti-CMV IgG titres to be associated with a higher risk of cardiovascular disease or mortality, while identifying CPR[4], IL-6 and TNF-α[15] and CD4/CD8-lymphocyte levels[18] as possible mediators. Other studies have been published that could not support these associations[16,20]. A 2017 meta-analysis by Wang et al. [19], found a 22% increased risk of future CVD in CMV-seropositive subjects, and estimated that 13.4% of CVD could be attributable to CMV; although quality of evidence was deemed low.
These findings were not confirmed in previous studies examining the BELFRAIL-cohort of 549 individuals aged 80 years or older in Belgium[21]. Matheï et al. found no association between CMV serostatus and all-cause mortality within this population, but did report a higher risk in subjects with a high anti-CMV IgG titre [22]. High levels of CRP were not significantly associated with positive CMV serology or high CMV IgG antibody titres and CMV serostatus was found to be negatively associated with frailty [3]. It seems the BELFRAIL cohort represents a subgroup of the general population i.e. the oldest old, in which abovementioned associations and its pathways do not fully apply. This cross-sectional study aims to further examine the role of CMV in cardiovascular disease, by studying the relation between CMV serostatus/titre and various cardiovascular morbidities. For this purpose, we also examined Ankle-Brachial Index (ABI) as a potential intermediate marker for atherosclerosis in its relationship to CMV.

Methodology

Study Population

This study is embedded within the BELFRAIL study, a prospective, observational, population-based cohort study of subjects aged 80 years and older in Belgium. All the participants in the study gave written informed consent, and the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL) of Brussels approved the study. The study design, methods and characteristics of the cohort were previously described in detail[21]. Briefly, 29 general practitioner (GP) centres included 567 subjects between November 2, 2008 and September 15, 2009. Only three exclusion criteria were used: dementia (defined as having a known mini mental state examination (MMSE) score < 15/30), palliative care, and presence of a medical emergency. Patients were questioned and examined by both a GP and a clinical research assistant (CRA). The GP recorded known cardiovascular risk factors and the previous medical history of the patient. Indicators of the cardiovascular risk profile were hypertension, hyperlipidaemia, type 2 diabetes mellitus, smoking (either current or ex-smoker) and BMI > 30. Cardiac morbidities were defined as a positive response for the history of angina pectoris or acute myocardial infarction, an episode of decompensated heart failure and a previous history of PTCA or stent and coronary surgery. Other cardiovascular morbidities consisted of previous TIA or CVA, known PAD and a previous history of arterial surgery. A compound variable for coronary heart disease was created, defined as history of either angina pectoris, acute myocardial infarction, PCI/stent or coronary surgery. The CRA performed an extensive examination containing performance testing, several questionnaires, and technical examinations. Women represented 63.1% (*n*=358) of the study population and had a mean age of 85.0 ± 3.9 years. Male participants had a mean age of 84.3 ± 3.3 years.

ABI data was recorded from a subgroup of patients (n=239) from a GP practice in Hoeilaart. ABI was measured by a trained GP with the aid of an automatic oscillometric appliance (SCVL-2007, Diegel Healthworks® and associated software). A value of 0.9 or more was viewed as normal, a value of less than 0.9 was considered a reduced ABI[23].

Laboratory analyses

A blood sample was collected on each patient after fasting (between 7.00 AM and 10.30 AM), and immediately stored in a refrigerated container until arrival in the central laboratory (< 3 h after blood collection). Plasma (EDTA, heparin) or serum samples were obtained after centrifugation and immediately stored frozen at -80°C until analysis.

The CMV IgG concentrations were measured on the ARCHITECT® i4000SR (Abbott Diagn, Abbott Park, Illinois, USA). The criteria for interpretation
were as follows: positive ≥6.0 AU/ml and negative <6 AU/ml. A large panel of inflammatory biomarkers and cytokines (12 Cytokines Array 1) was analyzed using Biochip arrays on the Evidence Investigator™ analyzer (Randox Laboratories Limited, Crumlin, UK). The UniCel®DxC 800 Synchron (Beckman-Coulter, Brea, USA) was used to measure ultrasensitive (us) CRP levels. Details on the analytical methods and detection limits were were previously published [21]. The hsCRP and anti-CMV IgG titre were transformed into a binary variable: cut-off values were established at 3.0mg/dL[24] for hsCRP and 250 IU/mL for anti-CMV IgG titre.

Statistical analysis

Continuous data are presented as the mean and standard deviation (SD, categorical data are presented as numbers and percentages. Comparisons between the different categories of subjects were performed using Student's t-test for continuous data, since only normally distributed data was used, and the $\chi 2$ tests or Fisher's exact test for categorical data. $P< 0.05$ was considered to be statistically significant.

Binary regression analysis was performed for both CMV serostatus and anti-CMV IgG titre using following dependent variables: ABI, angina pectoris, myocardial infarction, peripheral artery disease, TIA/stroke, cardiomyopathy, episode of decompensated heart failure, PCI/stent, coronary surgery, arterial surgery and a compound variable of coronary heart disease. Ordinal logistic regression was used for the number of cardiovascular diseases as dependent variable.

Gender, age, BMI, hypertension, hyperlipidaemia, diabetes, smoking status (past or present) and hsCRP were entered into both regression analyses as possible confounders. Interaction terms between anti-CMV serostatus/titre and hsCRP were tested, but not significant and therefore not included in the models. When a significant association between either CMV serostatus or anti-CMV IgG titre and the dependent variable was found, results were controlled using both forward and backward selection of co-variables. Hosmer and Lemeshow goodness-of-fit tests were performed in each model.

All statistical analyses were performed using IBM® SPSS® Statistics version 24.0.0.1 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

Characteristics	CMV negative	CMV positive	*P* value	Anti-CMV IgG < 250IU/ml	Anti-CMV IgG ≥ 250IU/ml	*P* value
Gender						
Male (*n*, %)	**65 (32)**	**138 (68)**	**0.023**	**96 (69.6)**	**42 (30.4)**	**0.034**
Female	78 (22.5)	268 (77.5)		157 (58.8)	110 (41.2)	
Age (mean, ±SD)	84.5 (±0.30)	84.8 (±0.18)	0.51	84.4 (±0.22)	85.5 (±0.31)	0.582
Cardiovascular risk profile						
BMI ≥30	42 (26.6)	116 (73.4)	0.869	71 (61.2)	45 (38.8)	0.740
Hypertension	100 (26.0)	284 (74.0)	0.702	177 (62.3)	107 (37.7)	0.543
Hyperlipidaemia	66 (27.8)	171 (72.2)	0.469	114 (66.7)	57 (33.3)	0.077
Diabetes	30 (29.7)	71 (70.3)	0.337	46 (64.8)	25 (35.2)	0.846
Smoker (current or ex)	48 (27.9)	124 (72.1)	0.560	77 (62.6)	46 (37.4)	0.733
Cardiovascular morbidities						
Angina pectoris	22 (24.2)	69 (75.8)	0.893	39 (56.5)	30 (43.5)	0.400
Myocardial infarction	18 (30.0)	42 (70.0)	0.670	30 (71.4)	12 (28.6)	0.376
PAD[1]	12 (24.5)	37 (75.5)	0.976	20 (54.1)	17 (45.9)	0.457
TIA[2] or stroke	26 (26.5)	72 (73.5)	0.843	39 (54.2)	33 (45.8)	0.103
Cardiomyopathy	15 (27.8)	39 (72.2)	0.750	21 (53.8)	18 (46.2)	0.217
Decompensated HF[3]	13 (22.0)	46 (78.0)	0.207	**20 (43.5)**	**26 (56.5)**	**0.002**
PCI[4] or stenting	10 (21.7)	36 (78.3)	0.536	23 (60.5)	15 (39.5)	0.795
Coronary surgery	10 (29.4)	24 (70.6)	0.560	14 (51.9)	13 (48.1)	0.238
Arterial surgery	4 (15.3)	22 (84.6)	0.395	15 (60.0)	10 (40.0)	0.792
Coronary Heart Disease	38 (27.3)	101 (72.7)	0.699	61 (60.4)	40 (39.6)	0.619
Number of CVD						
0	76 (26.2)	214 (73.8)	0.366	148 (69.2)	66 (30.8)	**0.008**
1	32 (27.4)	85 (72.6)		42 (49.4)	43 (50.6)	
2	16 (23.5)	52 (76.5)		31 (59.6)	21 (40.4)	
3	13 (32.5)	27 (67.5)		16 (59.3)	11 (40.7)	
4	1 (6.3)	15 (93.8)		12 (80.0)	3 (20.0)	
5	3 (30.0)	7 (70.0)		3 (42.9)	4 (57.1)	
6	1 (16.7)	5 (83.3)		1 (20.0)	4 (80.0)	
7	1 (100)	0		0	0	
hsCRP high titre	42 (23.0)	141 (77.0)	0.235	89 (63.1)	52 (36.9)	0.843
Interleukin-6						
Lowest tertile (<1.52)	34 (24.8)	103 (75.2)	0.982	59 (57.8)	43 (42.2)	0.211
Mid tertile	34 (24.6)	104 (75.4)		70 (67.3)	34 (32.7)	
Highest tertile (>2.76)	35 (25.5)	102 (74.5)		70 (68.6)	32 (31.4)	
ABI < 0.9	19 (27.5)	50 (72.5)	0.262	30 (60.0)	20 (40.0)	0.243
Total	143 (26.1)	405 (73.9)		253 (62.5)	152 (37.5)	

Table 1. Characteristics of the study population in function of CMV serostatus and CMV IgG titre.
[1]Peripheral artery disease; [2]Transient ischemic attack; [3]Heart failure; [4]Percutaneous coronary intervention

Results

Serological data was available for all 548 included patients; ABI data was available for 239 patients (48.3%). Seventy-four percent (*n* = 405) of the total cohort were found to be CMV seropositive, of whom 37.5% had an anti-CMV IgG >250 IU/ml (*n* = 152). A history of cardiovascular disease was present in 290 (47.9%) and 214 (47.8%) patients, respectively of the total cohort and the CMV-seropositive subgroup. Table 1 shows the characteristics of the study population, as compared between subgroups described above. A high anti-CMV IgG titre was found to have a statistically significant association with female gender, a previous episode of decompensated heart failure and the number of cardiovascular diseases. Regarding the traditional cardiovascular risk factors, no significant difference was found between subgroups.

Logistic regression was performed, further studying the association between CMV serostatus in the total population (*n*=548) or anti-CMV IgG titre in the CMV-positive population (*n*=405) on the one hand, and ABI, separate cardiovascular morbidities and the number cardiovascular disease on the other hand. Results are presented in table 2. After adjustment for confounding factors, no association with ABI could be identified in either group. In the CMV-positive subpopulation, the association between anti-CMV IgG titre and history of decompensated heart failure remained statistically significant, with an adjusted odds ratio (OR) of 2.52 (95% CI: 1.32 - 4.79). Ordinal logistic regression demonstrated a significant association between anti-CMV IgG titres and the number of cardiovascular diseases, with an adjusted OR of 1.81 (95%CI 1.21-2.72). Analogously, a high anti-CMV IgG titre increased the odds of history of any cardiovascular disease by a factor of 2.10 (95% CI: 1.35-3.27). In the same population, a trend towards significance was observed for history of TIA or stroke (OR 1.60; 95% CI: 0.93-2.74) and coronary surgery (OR 2.42; 95% CI: 1.00- 5.87). In the total population, CMV-seropositivity did not significantly increase the probability of history of any particular cardiovascular disease or the number of cardiovascular morbidities.

	CMV Serostatus (n=548*)		Anti-CMV IgG titre (n= 405*)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ABI[1]	0.69 (0.33-1.49)	0.353	1.52 (0.67-3.45)	0.315
MI[2]	1.13 (0.97-1.13)	0.720	0.72 (0.34-1.51)	0.380
PAD[3]	1.21 (0.59-2.46)	0.609	1.68 (0.81-3.48)	0.163
Angina Pectoris	1.22 (0.71-2.10)	0.475	1.38 (0.80 – 2.39)	0.247
Cardiomyopathy	1.05 (0.53-2.07)	0.888	1.52 (0.76-3.07)	0.239
TIA[4]/stroke	0.96 (0.58-1.60)	0.875	1.60 (0.93-2.74)	0.087
Decompensated HF[5]	1.17 (0.60-2.26)	0.643	**2.52 (1.32-4.79)**	**0.005**
PCI[6]/stent	1.68 (0.76-3.66)	0.188	1.35 (0.66-2.79)	0.41
Coronary surgery	1.36 (0.59-3.17)	0.470	2.42 (1.00-5.87)	0.050
Arterial surgery	2.44 (0.81-7.39)	0.114	1.32 (0.55-3.19)	0.538
Coronary Heart Disease	1.12 (0.70-1.78)	0.644	1.26 (0.77-2.08)	0.363
Number of cardiovascular diseases	1.26 (0.86-1.85)	0.232	**1.81 (1.21-2.72)**	**0.004**
Any cardiovascular disease	1.15 (0.76-1.73)	0.512	**2.10 (1.35-3.27)**	**0.001**
≥2 cardiovascular diseases	1.35 (0.83-2.18)	0.229	1.42 (0.87-2.34)	0.163

Table 2. Logistic regression results, presented as Odds Ratios (OR) and 95% confidence interval (CI).
** Regression analysis using ABI as dependent variable were carried out on a subpopulation of 239 subjects.*
[1]Ankle-Brachial Index; [2]Myocardial infacrtion;[3] Peripheral Artery Disease; [4]Transient ischemic attack; [5]Heart failure; [6]Percutaneous coronary intervention

Discussion

In this cross-sectional study of a representative cohort of 548 community-dwelling Belgian subjects aged 80 years or more, no association between CMV serostatus and the history of cardiovascular disease could be identified. However, within the CMV-seropositive subpopulation, individuals with high anti-CMV IgG titres (>250IU/mL) were found to have a higher number of cardiovascular morbidities in their medical history. These findings seem to be in accordance with previous results of a study of the same cohort by Matheï et al.[22], which demonstrated CMV-seropositive individuals with high anti-CMV IgG titres to be at higher risk for all-cause mortality in a three-year follow up period, compared to those with lower titres. Similar to the observations made in that publication, our data seem to be in contrast with the findings of most studies on this subject. A 2017 meta-analysis reported CMV seropositivity to be associated with a 22% increase in risk of cardiovascular diseases[19]. However, the included studies primarily used cardiovascular death as outcome; results for ischemic heart disease and stroke did not reach significance. We suspect these seemingly contrasting findings to be at least partially attributable to a survival effect. Few studies have been carried out focusing on the oldest old. In fact, we only found one previous publication using a exclusively octogenarian population, which found CMV seropositivity to be associated with a higher prevalence of ischemic heart disease, but not with any other cardiovascular disease[18].

We also observed a significant association between high anti-CMV IgG titres among CMV seropositives and history of decompensated heart failure, but no other individual cardiovascular diseases. No relation between anti-CMV serostatus/titre and ABI could be demonstrated. The positive association between anti-CMV IgG titre and history of coronary surgery was only marginally insignificant. These results can be considered surprising, given that most of the current evidence postulates the influence of CMV on atherosclerosis to be the main cause of the effect of CMV on cardiovascular morbidity and mortality.

Indeed, most research focuses on the role of CMV in atherosclerosis, being the primary cause of CVD[25]. The aetiology of atherosclerosis is a complex phenomenon, involving the interaction of lipoproteins, vascular wall components, blood cells, and both the cellular and humoral immune system[26]. Multiple possible mechanisms have been proposed concerning the influence of CMV on atherosclerosis[2], but for now remain incompletely unravelled. Inflammation has been recognised to be a central process in the formation and progression of atherosclerotic plaques, and CRP (and IL-6 and TNF-α to lesser extent) is an important predictor of cardiovascular risk[26,27].

Several studies have reported a mediating role for CRP in the interaction between CMV and cardiovascular disease, most focusing on mortality as outcome. In the NHANES III study population, consisting of 14153 subjects between 25 and 90 years of age, Simanek et al.[4] found high CRP levels within seropositive subjects to be associated with a 25.9% higher risk for CVD-related mortality, demonstrating the relationship between CMV and mortality to be partially mediated by CRP. However, CMV's main impact on mortality was seen in individuals aged 55–75 at the time of the survey whereas CMV imposed little increased risk in the most elderly (aged 75–90). Again, these findings could not be confirmed in our BELFRAIL population: although both serum IL-6 and CRP were found to be strongly associated with all-cause mortality[28], neither positive CMV serology results nor high anti-CMV IgG titres were found to be significantly associated with CRP or serum IL6 levels[3]. The associations found in the current study were independent of CRP levels, however due to the study design no conclusions can be drawn concerning the role of CRP as possible mediator (see below: limitations).

CMV has also been shown to increase the age-related process of immunosenescence: the age-related deterioration of immune-competence, characterized by decrease in naïve T cells and increase in memory T cells, causing a compromised immune response [29,30]. The Swedish OCTA/NONA longitudinal studies of elderly Swedes found CMV seropositivity to be associated with the presence of an Immune Risk Profile (IRP) in very old individuals[31,32], which in turn was found to increase all-cause mortality. The IRP is characterised by an inverted CD4/CD8 ratio and a low number of B-cells, resulting in poor T-cell response to pathogens[33]. The immune-related association between CMV and cardiovascular disease is less studied. Spyridopoulos et al.[18,34] suggested that senescent alterations caused by CMV in the CD4 and CD8 T-cell compartments to be associated with telomere dysfunction, MAP-kinase activation and mitochondrial dysfunction, which in turn cause hypersecretion of pro-inflammatory cytokines contributing to vascular endothelial dysfunction and atherosclerosis. In a BELFRAIL-population study[35], CMV seropositivity was indeed inversely associated with the CD4:8 ratio, but highest mortality rates were seen among CMV-positive women (but not men) with higher CD4:8 ratios. Mediation analysis did not show the association between CMV and mortality to be mediated through its effect on the CD4:8 ratio, contrary to the findings of the OCTA/NONA studies. The Leiden 85+ study of individuals 88 years or older also reported a lower frequency of naïve CD8+ T cells at baseline correlated with significantly better survival[36].

The fact that observations made in the general population have not been unambiguously reproduced in studies in the oldest old, may be ascribed to a survival effect. Individuals less susceptible to the adverse effect of CMV infection could be naturally selected an thus over-represented in the BELFRAIL study population, and by extension the very old population in general. In this perspective, circulating anti-CMV IgG antibodies might represent a more valuable measure than CMV serostatus alone; because they may reflect the host's ability to restrain CMV infection and might correlate with reactivation of the virus, although this has not been proven. The way the immune system interacts with the virus, rather than the presence of the virus itself, might determine whether the host develops adverse effect from the infection[22]. In support of this theory, Derhovanessian et al[37]. found offspring of longevity families to be less susceptible to the characteristic CMV-associated immune alterations. Our results, showing high anti-CMV IgG titres, but not serostatus, to be associated with cardiovascular disease also support this hypothesis; although we are not able to elucidate the pathway through which this association takes effect. High-quality longitudinal studies with prolonged follow-up periods are needed to determine whether a direct causative relation between CMV infection and cardiovascular and other diseases exists. They also need to distinguish between CMV serostatus and antibody concentrations in clarifying the mechanisms of interaction between the virus and its host. Given the high world-wide prevalence of CMV-infection and increasing longevity, targeting CMV in possible therapeutic or preventive interventions might have an unexpectedly large influence on disease burden in the older population.

Strengths and limitations

This study has several strengths. First, a large population- based sample designed to be representative of community- dwelling adults aged 80 and older in Belgium was used. Secondly, although chronic CMV infection is prevalent worldwide, especially in older individuals, the CMV seroprevalence in the BELFRAIL study (76%) was only moderately higher than the seroprevalence rates in elderly populations that have been observed in other studies. The lower probability of being CMV positive increased the power to make statistical inferences.

Several limitations must also be considered. First of all, cardiovascular diseases presented before the time of assessment. Consequently, no information is available on the time between CMV infection and development of CVD. Furthermore, we cannot determine whether CMV infection preceded the reported diseases. Second, the cardiovascular diseases were reported by the GP rather than assessed by the researchers, possibly in resulting in underdiagnosis of subclinical and less likely, overdiagnosis. Third, residual confounding might have affected the results. We corrected for traditional cardiovascular risk factors[38,39]. However, studies have shown these are less appropriate in predicting cardiovascular disease and mortality in an older population. Finally, any interpretation of the results need to take survival selection into account.

Conclusions

In this cross-sectional study of a representative sample of 548 individuals aged 85 years or older, high anti-CMV IgG titres were significantly associated with a higher number of cardiovascular diseases and the history of decompensated heart failure among CMV-seropositive subjects. CMV serostatus was not related to the number of CVD, nor to any particular CVD. In our population of oldest old, the level of anti-CMV IgG antibodies seems to hold a stronger association with adverse outcomes than CMV serostatus itself, possibly implicating the role of disease reactivation.

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Bijlage 1. Goedgekeurd protocol

Cytomegalovirus en cardiovasculaire aandoeningen: literatuurstudie en analyse van gegevens uit de BELFRAIL-databank

Student(en): Niels Vranckx
Faculteit: Geneeskunde
Opleiding: Master in de huisartsgeneeskunde (Leuven e.a.)
Het onderzoek is: monocentrisch
De opdrachtgever is: academisch (universiteit,...)
Het onderzoek is: Overige.

Bijkomende gegevens:
Achtergrond:

In de laatste jaren werd aangetoond dat CMV infectie mogelijks een rol zou kunnen spelen in verschillende chronische aandoeningen via een proces van chronische inflammatie. Echter lijkt deze interactie zeer complex en ontbreekt er éénduidige evidentie over de invloed van CMV op functionaliteit/mortaliteit op in een oude populatie.
De relatie tussen CMV en endotheliale dysfunctie/atherosclerosis lijkt het meest uitvoerig beschreven in de literatuur.
Het doel van deze studie is uitzoeken welke verschillende pathways hiervoor reeds onderzocht werden en of deze relatie ook aangetoond kan worden binnen de BELFRAIL-cohort van 80-plussers.

Background - BELFRAIL Cohort

In coming decades the proportion of very elderly people living in the Western world will dramatically increase. This forthcoming "grey epidemic" will lead to an explosion of chronic diseases. In order to anticipate booming health care expend itures and to assure that social security is funded in the future, research focusing on the relationship between chronic diseases, frailty and disability is needed. The general aim of the BELFRAIL cohort study (BFC80+) is to study the dynamic interaction between health, frailty and disability in a multi-system approach focusing on cardiac dysfunction and chronic heart failure, lung function, sarcopenia, renal insufficiency and immunosenescence.

Vraagstelling:

Welke pathways voor een associatie tussen CMV seropositiviteit en cardiovasculaire morbiditeit/mortaliteit worden beschreven in de literatuur?

Welke evidentie bestaat er reeds rond de associatie tussen CMV en cardiovasculaire aandoeningen?

Kan deze evidentie gereproduceerd worden met de gegevens beschikbaar in de BELFRAIL-cohort (80j en ouder)?

Methodologie:

- Niet-systematisch literatuuronderzoek

- Analyse van reeds beschikbare gegevens binnen de BELFRAIL-databank. Geen bijkomende interventies.

Referenties:

The BELFRAIL (BFC80+) study: a population-based prospective cohort study of the very elderly in Belgium. Vaes B, Pasquet A, Wallemacq P, Rezzoug N, Mekouar H, Olivier PA, Legrand D, Matheï C, Van Pottelbergh G, Degryse J. BMC Geriatr. 2010 Jun 17;10:39.

Informed consent / vragenlijsten / interviewprotocols:
Promotor:

Cathy Matheï (catharina.mathei@kuleuven.be - u0009104 - Acad. Centr. voor Huisartsgeneeskunde)
Registratienummer:
mp19399

Bijlage 2. Gunstig advies Ethisch Comité

Geachte Heer/Mevrouw De Opleidingspecifieke Ethische Begeleidingscommissie van de opleiding "Master in de huisartsgeneeskunde (Leuven e.a.)" heeft uw voorstel tot Masterproef "Cytomegalovirus en cardiovasculaire aandoeningen: literatuurstudie en analyse van gegevens uit de BELFRAIL-databank" onderzocht en gunstig geadviseerd. Dit betekent dat de commissie van oordeel is dat de studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Dit gunstig advies van de commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor zelf verantwoordelijk. Indien u van plan bent uw masterproef te publiceren kan deze e-mail dienen als bewijs van goedkeuring.

Dear Mr/Ms The Supervisory Committee on Medical ethics of the "Master in de huisartsgeneeskunde (Leuven e.a.)" programme has reviewed your master's thesis project proposal "Cytomegalovirus en cardiovasculaire aandoeningen: literatuurstudie en analyse van gegevens uit de BELFRAIL-databank" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent.

Opleidingsspecifieke begeleidingscommissie van de opleiding Master in de huisartsgeneeskunde (Leuven e.a.)