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Caregiver burden and fatigue in caregivers of people with dementia: Measuring human herpesvirus (HHV)-6 and -7 DNA levels in saliva

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ABSTRACT

Purpose: We examined chronic fatigue, which has not been investigated in detail, in family caregivers for people with dementia.
Methods and materials: Forty-four community-dwelling family caregivers (the caregiver group: CG) and 50 elderly control participants (the non-caregiver group: NCG) participated in this study. We measured salivary human herpesvirus (HHV)-6 and -7 DNA levels and the Chalder fatigue scale (CFS) to assess levels of fatigue; we also measured the Center for Epidemiologic Studies-Depression Scale, Physical Activity Scale for the Elderly, Zarit Caregiver Burden Interview, Mini-Mental State Examination, Assessment of Motor and Process Skills, and Dementia Behavior Disturbance Scale.
Results: For CG, the salivary HHV-6 DNA levels and CFS scores were significantly higher than those in NCG. The salivary HHV-6 DNA levels in CG were significantly correlated with depressive symptoms, the cognitive function of the patients, and the activities of daily living/instrumental activities of daily living (ADL/IADL) abilities of the patients. The CFS scores in CG significantly correlated with caregiver burden, depression symptoms, leisure physical activity, the number of other family caregivers, and the hours spent for caregiving per week, as well as with behavior disturbances and ADL/IADL abilities.
Conclusions: The salivary HHV-6 DNA levels may be added as a new biomarker for caregiver exhaustion. We concluded that fatigue assessments should be performed by not only a questionnaire, such as the CFS, but also by a biomarker search, such as HHV-6, when estimating the caregiver burden for family caregivers of people with dementia.

1. Introduction

The caregiver burden in caregivers of people with dementia is one of the most serious problems in medical and nursing care for dementia (Brodaty & Donkin, 2009). According to chronic stress for caregiving, it is reported that caregivers' mortality (Schulz & Beach, 1999) and risk of coronary heart disease is increased (Lee, Colditz, Berkman, & Kawachi, 2003). The Zarit Caregiver Burden Interview (ZBI; Zarit, Reever, & Bach-Peterson, 1980) has been used for the assessment of family caregiver burden in people caring for patients with dementia. ZBI estimate caregiver stress from caregiving, economic burden, or restriction of social participation. ZBI, however, is not enough to assess for caregivers' health, because it is a questionnaire that evaluates subjective caregiver burdens instead of objective burdens.

In the current study, we focused on fatigue in family caregivers. Fatigue is defined as an inimitable discomfort and a condition of decreased physical activity with a desire for rest; it is caused by excessive physical and mental activity or disease. Fatigue, pain, and fever are the three alarms for an organism in crisis. We considered that fatigue was a useful indicator that assessed the health risk caused as a result of chronic stress from caregiving. In previous studies of the burden on family caregivers of patients with

Abbreviations: CG, the caregivers group; NCG, the non-caregiver group; HHV, human herpesvirus; DNA, deoxyribonucleic acid; CFS, Chalder fatigue scale; CFS-P, CFS-physical; CFS-M, CFS-mental; CES-D, the Center for Epidemiologic Studies-Depression Scale; PASE, Physical Activity Scale for the Elderly; PASE-L, PASE-leisure; PASE-H, PASE-house; PASE-W, PASE-work; ZBI, Zarit Caregiver Burden Interview; MMSE, Mini-Mental State Examination; AMPS, Assessment of Motor and Process Skills; DBD, Dementia Behavior Disturbance Scale; ADL, activities of daily living; IADL, instrumental activities of daily living; QOL, quality of life; PCR, polymerase chain reaction; SD, standard deviation; IQR, interquartile range.

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dementia, fatigue has been assessed as a part of the quality of life (QOL) assessment; but fatigue itself has not been investigated in detail. In this study, we proposed to evaluate fatigue in these family caregivers using two scales.

Firstly, we used the Chalder Fatigue Scale (CFS; Chalder et al., 1993), which is a self-reported assessment and has often been used to assess patients with chronic fatigue syndrome (Morriss, Wearden, & Mullis, 1998). Secondly, we measured the saliva DNA levels for human herpesvirus (HHV)-6 and -7. Most people get infected with HHV-6 and -7 during childhood, and life-long latency is established (Kondo & Yamanishi, 2007). The trigger that induces viral reactivation has not been completely identified. However, it is reported that when physical and mental stress result in fatigue, human herpesvirus may be autonomously reactivated and shed in the saliva (Kondo & Yamanishi, 2007; Whitley, Kimberlin, & Prober, 2007). Assessment of fatigue by using the salivary HHV-6 and -7 DNA levels has not been standardized. However, in a few previous studies, it has been reported that HHV-6 and -7 DNA saliva levels are useful for the assessment of chronic fatigue (Fukuda et al., 2015; Ito et al., 2014; Morris, Berk, Walder, & Maes, 2015; Tanaka, Shigihara, Funakura, Kanai, & Watanabe, 2012). Acute stress does not influence these levels, and diurnal variation is little (Kondo, 2009). We surmised that the HHV-6 and -7 DNA levels in the saliva were relevant in the assessment of caregivers who were exposed to moderate- to long-term stress during caregiving.

In this study, we examined the levels of fatigue which has not been investigated in detail in the family caregivers of patients with dementia. In particular, we also wanted to investigate the usefulness of the salivary HHV-6 and -7 DNA levels as a new fatigue biomarker.

2. Methods

2.1. Subjects

We recruited 44 primary family caregivers that were caring for relatives with dementia (the caregiver group: CG). Caregivers with intellectual problems were excluded. The people with dementia had been diagnosed by psychiatrists. Fifty non-caregiver controls (the non-caregiver group: NCG) were recruited from the senior school in the same area as the psychiatric hospital. Those who were caring for someone already were excluded.

This study was approved by the Ethical Committee of Kobe Gakuin University in December 2013 [approval number HEB131218-1] and the Ethics Committee of the Jikei University School of Medicine in February 2015 [approval number 23-316 (7822)]. All participants provided written informed consent to participate in the study.

2.2. Assessments

For this cross-sectional study, we collected data between January and April 2015. The evaluations of the people with dementia had been obtained by an occupational therapist in the psychiatric hospital. The questionnaires were self-reported from home, and the saliva samples were either collected during the time that questionnaires were distributed or collected at home or the psychiatric hospital or school.

Saliva samples for the analysis of the HHV-6 and -7 DNA levels were collected in a tube (Sallivette; Sarstedt, Tokyo, Japan) and centrifuged at 3000*g* for 2 min at 4 °C. These supernatants were dispensed at 450 μl and stored at −8 °C until analyzed. The DNA samples were extracted from 400 μl of saliva with an EZ1 Virus Mini Kit v2.0 (Qiagen, California, USA). DNA was eluted in 90 μl of elution buffer. The HHV-6 and -7 DNA levels were quantified via real-time polymerase chain reaction (PCR), which was completed using an Applied Biosystems 7300 Apparatus (Life Technologies, California, USA). The amplifications were performed in duplicate in a total volume of 50 μl containing 25 μl of Premix Ex Taq (Perfect Real Time; Takara Bio Inc., Shiga, Japan), 0.45 μl of PCR forward primer (100 μM), 0.45 μl of PCR reverse primer (100 μM), 1.25 μl of TaqMan probe (10 μM), 1 μl of Rox reference dye, 5 μl of the viral DNA, and 16.85 μl of PCR-grade water. The primers used for real-time PCR were as follows: HHV-6 forward primer, 5′-GACAATCA-CATGCCTGGATAATG-3′; HHV-6 reverse primer, 5′-TGTAAGCGTGTGGTAATGGACTAA-3′; HHV-6 probe, 5′ -FAM-AGCAGCTGGCGAAAAGTGCTGTGC-TAMRA-3′; HHV-7 forward primer, 5′-CGGAAGTCACTGGAGTAATGAC-3′; HHV-7 reverse primer, 5′-CCAATCCTTCCGAAACCGAT-3′; and HHV-7 probe, 5′-FAM-CCTCGCAGATTGCTTGTTGGCCATG-TAMRA-3′ (Gautheret-Dejean et al., 2002; Hara et al., 2002). The thermal profile was 95 °C for 30 s, followed by 50 cycles of 95 °C for 5 s and 60 °C for 31 s. Data analysis was performed using Sequence Detection Software version 1.4 (Life Technologies, California, USA). The sample below the detection limits (20 copies/mL) adopted the detection limit value. The HHV-6 and -7 DNA levels (copies/mL) were log-transformed (log 10).

The Chalder Fatigue Scale (CFS) for chronic fatigue assessment contained 14 items, which had been divided into two subscales: physical symptoms (CFS-P) and mental symptoms (CFS-M). Each answer was scored from 0 to 3. The CFS-P contained eight items (score range; 0–24), and the CFS-M contained six items (score range; 0–18). A higher score indicated that the level of fatigue was severe. In this study, we assessed the participants using the subscales (CFS-P, CFS-M).

We also used other assessments during the study. Depressive symptoms were assessed by the Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977), which contained 20 items (score range; 0–60); a score of over 16 points was graded as being depressed. Physical activity levels for the past week were assessed by the Physical Activity Scale for the Elderly (PASE; Hagiwara, Ito, Sawai, & Kazuma, 2008), which had 12 components pertaining to leisure time activity (PASE-L; five components), household activity (PASE-H; six components), and work-related activity (PASE-W; one component) over the past seven days.

In addition, four assessments were carried out in CG. The caregiver burden was assessed using the ZBI, and the cognitive functioning of the patients with dementia was assessed with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Daily living/instrumental activities of daily living (ADL/IADL) score for the people with dementia was assessed using the Assessment of Motor and Process Skills (AMPS; Fisher & Bray, 2012), which was an observational evaluation used by occupational therapists in the evaluation of the quality of ADL/IADL. The motor ability (need for physical effort) and process ability (efficiency) were computed from the raw scores by the AMPS computer-scoring software. Eighty-six percent of persons with motor ability measures above 1.5 logits and process ability measures above 1.0 logits can be independent in the community. Behavior disturbances for people with dementia were assessed using the Dementia Behavior Disturbance Scale (DBD 13; Machida, 2012), which contained 13 items (score range; 0–52). Higher scores indicated more severe behavioral disturbances.

2.3. Statistical analysis

Statistical analyses were carried out using SPSS version 17.0. (IBM, New York, USA). A P value of <0.05 was considered statistically significant. The Shapiro–Wilk test was used for the test of normality. The t-test, Mann–Whitney test, or Chi-Square test was used for the comparisons between CG and NCG. In all subjects or in CG, we computed the Pearson's partial correlation