Centers of Advanced Medicine
Center for Medical Science of Fatigue

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General Summary

The Jikei Center for Medical Science of Fatigue (JCMSF) was established in 2014 with support from the Ministry of Education, Culture, Sports, Science and Technology–Supported Program for the Strategic Research Foundation at Private Universities. The JCMSF is aimed at contributing to human welfare through developing novel methods for the diagnosis, prevention, and care of fatigue-related diseases. For this aim, our research focuses on the mechanism of fatigue and fatigue-related diseases.

Fatigue is caused by many different factors, including sleep deprivation, persistent mental activity, and prolonged physical exertion. Long-term fatigue is reportedly experienced by at least 50% of workers in Japan and can cause cardiovascular dysfunction, such mental health disorders as depression, and occupational sudden death (*karoshi*).

Fatigue levels are frequently assessed with self-reporting questionnaires of feelings of fatigue, such as the Checklist Individual Strength and the Profile of Mood States, or with visual analog scales. However, negative or positive events at work are associated with the feeling of fatigue, and compensation practices within some industries tend to motivate individuals to distort their self-reported fatigue levels. Therefore, an individual's perception of fatigue may not be a correct indicator of fatigue.

Fatigue is associated with a perception of fatigue mediated by signaling pathways in the central nervous system. The mechanism for perceiving fatigue is thought to be associated with changes in levels of inflammatory cytokines and with changes in the autonomic nervous system. Because no objective measure of fatigue is universally accepted, serum inflammatory cytokine levels and neurobehavioral assays, such as psychomotor vigilance tests, are frequently used as biomarkers for fatigue.

Work-induced fatigue is frequently confused with pathological fatigue, such as chronic fatigue syndrome (CFS). The CFS is triggered by infection rather than overwork, and the diagnostic criteria for CFS are 6 months of unexplained fatigue that is not alleviated by rest and the presence of 4 of 8 additional symptoms (e.g., unrefreshing sleep, sore throat, and muscle pain). The CFS is thought to affect 1 to 8 of every 1,000 adults in the United States. Biomarkers proposed for diagnosing CFS have included cytokines, adrenergic genes, immunological markers, and cortisol. However, most of these markers are common to physiological fatigue, and even with these biomarkers distinguishing CFS and physiological fatigue is difficult.

When JCMSF was established it focused on indentifying biomarkers that could be used to distinguish physiological fatigue from pathological fatigue. We examined the amounts of salivary human herpesvirus (HHV) 6 and HHV-7 due to training in members of JCMSF. Because fatigue scores increased during training, we believed training provided sufficient physiological fatigue loading. The amounts of salivary HHV-6 and HHV-7 DNA

increased with training and decreased with rest, suggesting their usefulness as biomarkers of physiological fatigue. The amounts of HHV-6 and HHV-7 were also correlated with working time; however, they were not reactivated by pathological fatigue. These findings suggest that HHV-6 and HHV-7 are reactivated by physiological fatigue but not by pathological fatigue.

Research Activities

HHV-6 and HHV-7 are biomarkers for fatigue which distinguish between physiological fatigue and pathological fatigue

Fatigue reduces productivity and is a risk factor for lifestyle diseases and mental disorders. Physiological fatigue occurs in everyone but decreases with rest. Pathological fatigue, however, greatly reduces quality of life and requires therapeutic interventions. Therefore, these 2 types of fatigue must be distinguished, but biomarkers for distinquishing them have not been identified. We report on the measurement of salivary HHV-6 and HHV-7 as biomarkers for quantifying physiological fatigue. We observed that salivary HHV-6 and HHV-7 increased with military training and work and rapidly decreased with rest. Our results suggest that macrophage activation and differentiation are necessary for virus reactivation. However, HHV-6 and HHV-7 did not increase in subjects with obstructive sleep apnea syndrome, CFS, and major depressive disorder, which are thought to cause pathological fatigue. Thus, HHV-6 and HHV-7 would be useful biomarkers for distinguishing between physiological fatigue and pathological fatigue. Our findings suggest a fundamentally new approach to evaluating fatigue and preventing fatigue-related diseases.

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

Purpose: We examined chronic fatigue, which has not been investigated in detail, in caregivers for family members with dementia.

Methods: The subjects of this study were 44 community-dwelling family caregivers and 50 elderly persons who were not caregivers. We measured salivary levels of HHV-6 and HHV-7 DNA and used the Chalder Fatigue Questionnaire (CFQ) to assess levels of fatigue; we also used the Center for Epidemiologic Studies Depression Scale, the Physical Activity Scale for the Elderly, the Zarit Caregiver Burden Interview, the Mini-Mental State Examination, the Assessment of Motor and Process Skills, and the Dementia Behavior Disturbance Scale.

Results: The salivary HHV-6 DNA levels and the CFQ scores were significantly higher in caregivers than in elderly persons. The salivary HHV-6 DNA levels in caregivers were significantly correlated with depressive symptoms, the cognitive function of the family members with dementia, and the activities of daily living/instrumental activities of daily living abilities of the patients. The CFQ scores in caregivers significantly correlated with caregiver burden, depression symptoms, leisure physical activity, the number of other family caregivers, the hours spent by caregiving per week, behavior disturbances, and activities of daily living/instrumental activities of daily living abilities.

Conclusions: The salivary HHV-6 DNA level is a new biomarker for caregiver exhaustion. To estimate the burden of caregivers of family members with dementia, fatigue assessments should be performed with a questionnaire, such as the CFQ, and the search for a biomarker, such as the salivary HHV-6 DNA level.