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

Effects of Nutritional Supplementation on Fatigue, and Autonomic and Immune Dysfunction in Patients with End-Stage Renal Disease: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Fatigue is a predictor of cardiovascular events in patients with end-stage renal disease (ESRD) undergoing hemodialysis treatment. We hypothesized that multinutritional support would improve quality of life, fatigue symptoms, and potential quantitative measures including endocrine, immune and autonomic functions in patients with ESRD undergoing hemodialysis.

Two hundred and two hemodialysis patients were randomly assigned to receive active treatment (containing vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, carnitine, coenzyme Q10, naïve galacto-oligosaccharide, and zinc) or placebo after each dialysis session for 12 weeks. The patients and attending physicians were blinded to the treatment, and 172 patients (86 in each group) completed the study. Fatigue was evaluated via fatigue questionnaire at 0, 4, and 12 weeks. To assess human herpes virus (HHV) 6 and 7 reactivation, numbers of viral DNA copies were determined in saliva by polymerase chain reaction at weeks 0 and 12. Autonomic function was determined via measurement of beat-to-beat variation by using acceleration plethysmography.

Clinical characteristics, changes in fatigue, quality of life score, endocrine functions, and laboratory data did not differ significantly between the two groups. Several parameters of heart rate variability significantly increased after nutritional treatment compared to placebo. Nutritional drink for 12 weeks significantly suppressed HHV7 DNA copy numbers. Similarly, HHV6 DNA copy numbers tended to be decreased by treatment but without reaching statistical significance.

Nutritional supplementation may modulate immune and autonomic dysfunction in ESRD patients undergoing hemodialysis.

Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy—the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy

Chemotherapy improves the outcome of cancer treatment, but patients are sometimes forced to discontinue chemotherapy or drop out of a clinical trial due to adverse effects, such as gastrointestinal disturbances and suppression of bone marrow function. The objective of this study was to evaluate the safety and effectiveness of a mushroom product, active hexose correlated compound (AHCC), on chemotherapy-induced adverse effects and quality of life (QOL) in patients with cancer. Twenty-four patients with cancer received their first cycle of chemotherapy without AHCC and then received their second

cycle with AHCC. During chemotherapy, we weekly evaluated adverse effects and QOL via a blood test, EORTC QLQ-C30 questionnaire, and DNA levels of herpes virus type 6 (HHV-6) in saliva. The DNA levels of HHV-6 were significantly increased after chemotherapy. Interestingly, administration of AHCC significantly decreased the levels of HHV-6 in saliva during chemotherapy and improved not only QOL scores in the EORTC QLQ-C30 questionnaire but also hematotoxicity and hepatotoxicity. These findings suggest that salivary HHV-6 levels may be a good biomarker of QOL in patients during chemotherapy, and that AHCC may have a beneficial effect on chemotherapy-associated adverse effects and QOL in patients with cancer undergoing chemotherapy.