CHRONIC POST-INFLAMMATORY FATIGUE IN SARCOIDOSIS : FROM CYTOKINES TO BEHAVIOR

Ingrid Korenromp

June 28th, 2011

Promotors: prof dr CJ Heijnen, PhD; prof dr D Biesma, MD PhD

Co-promotors: dr A Kavelaars, PhD; dr OJM Vogels, MD PhD

Sarcoidosis is a systemic inflammatory disorder that is characterized by granuloma formation in different organs. Sarcoidosis patients frequently report fatigue. Even when the clinical symptoms of the inflammatory disease sarcoidosis have resolved, chronic fatigue may persist. In this study 75 patients with sarcoidosis in clinical remission were evaluated. Median time since diagnosis was 9 years (interquartile range 5 – 17). Chronic fatigue was present in 49% of patients. The fatigued patients reported significantly more pain points, lower scores on health status, higher levels of psychological distress, higher scores the personality trait Harm-Avoidance, a higher percentage of days awaking unrefreshed, and lower scores on muscle strength tests (respiratory muscles, handgrip and quadriceps) than the non-fatigued patients. Criteria for Chronic Fatigue Syndrome were met in 47% of fatigued cases. Compared to normscores, fatigued patients showed significantly reduced physical activity levels as measured with an accelerometer.

Immunologically, - after in vitro stimulation of supernatants of whole blood cultures – a complex of T cell produced cytokines/chemokines was identified which consisted of interleukin (IL)-4, IL-5 and IL-10. This so called Th2-complex was negatively associated with chronic fatigue. In addition, in fatigued patients in vitro production of monocyte-derived IL-8 was higher while plasma levels of MCP-1 was lower compared to non-fatigued patients. This observation led to the hypothesis that fatigued patients had been sensitized by the immense inflammation during the active phase of sarcoidosis. This sensitization of the neuronal system together with the reduced capability to produce Th2 cytokines (this Th2 response is necessary to

restore the immune balance) contributes to the persistence of chronic fatigue, even after the clinical signs of disease activity have resolved.
Furthermore, in response to acute psychosocial stress (Trier Social Stress Test) fatigued patients released less epinephrine than non-fatigued patients. Fatigued female patients also tended to have overall lower blood pressure levels compared to non-fatigued females. Moreover, compared to controls AUC's and N2P2-amplitudes of EEG recorded Laser Evoked Potentials of the study group were decreased while N2- and P2-latencies were normal. The latter finding points to reduced nociception via small Aδ-fibers, without damage of the myeline layer that surrounds the fibers.
At one year follow up in 50% of the study cohort reported chronic fatigue. Multiple regression analysis revealed that the cytokine/chemokine profile and psychoneurotic distress were significant predictors of fatigue severity as measured at follow up. As chronic post-inflammatory fatigue is a severe problem which persists over many years, accurate treatment is of the utmost importance. Therefore, we recommend a trial to assess the usefulness of cognitive behavior therapy (in order to alleviate psychological symptoms) in combination with graded exercise therapy (so as to enhance physical activity levels and muscle force, but also to stimulate sympathetic output and epinephrine secretion, which subsequently enhances Th2 cytokine production) in a group of chronically fatigued sarcoidosis patients in clinical remission.