The handle http://hdl.handle.net/1887/66270 holds various files of this Leiden University dissertation.

**Author:** Bouwens, J.A.
**Title:** Neuropsychiatric symptoms and immune system parameters in Huntington’s disease
**Issue Date:** 2018-10-18
Disease stage and plasma levels of cytokines in Huntington’s disease: a 2-year follow-up study

J.A. Bouwens, E. van Duijn, C.M. Cobbaert, R.A.C. Roos, R.C. van der Mast, E.J. Giltay
BACKGROUND

It has been shown that plasma levels of cytokines are elevated in Huntington’s Disease (HD) gene expansion carriers compared to controls, and are higher in advanced disease stages (1). To test the hypothesis that plasma cytokines may serve as a biomarker of disease progression (2), levels of pro-inflammatory and anti-inflammatory cytokines were measured in different disease stages at baseline and during the 2-year follow-up.

METHODS

In a cohort of 124 HD gene expansion carriers [described in (3)], of whom 92 could be reassessed at 2-year follow-up, plasma levels of tumor necrosis factor α (TNF-α), interleukin (IL)-1b, IL-1 receptor antagonist (ra), IL-5, IL-6, IL-8, and IL-10 were measured. High sensitivity (hs) ELISA assays were used to measure TNF-α, IL-1b, IL-6, and IL-10. Coefficients of variation ranged from 5.9-64%. The diagnostic confidence level (CL) of the Unified Huntington’s Disease Rating Scale (UHDRS) was used to define pre-motor symptomatic (CL 0-1) and motor symptomatic (CL 2-4) HD (5). The disease burden score (6), the Total Functional Capacity (TFC) scale (4), and the Total Motor Score (TMS) of the UHDRS were used as measures of disease progression. To assess longitudinal changes, paired-sample t-tests were used. Group comparisons were conducted using independent sample t-tests. Associations between disease stage and cytokine levels were analyzed using data from both assessments by multilevel analysis, accounting for covariance.

RESULTS

At baseline, the average age of participants was 49 years, 56% were male and 27% were pre-motor symptomatic. During the 2-year follow-up, increases were found in the levels of TNF-α [1.48 pg/mL standard error (SE) 1.05 pg/mL vs. 1.65 pg/mL SE 1.06 pg/mL, p=0.01] and IL-10 (0.38 pg/mL SE 1.03 pg/mL vs. 0.41 pg/mL SE 1.03 pg/mL, p=0.04). Motor symptomatic participants had higher levels of IL-6 than pre-motor symptomatic participants (0.98 pg/mL SE 1.06 pg/mL vs. 0.64 pg/mL SE 1.07 pg/mL, p=0.007). Levels of IL-5 were lower in motor symptomatic compared with pre-motor symptomatic participants (0.075 pg/mL SE 1.25 pg/mL vs. 0.151 pg/mL SE 1.25 pg/mL, p<0.001).

With regard to measures of disease progression, only the levels of IL-6 and IL-8 were inversely associated with the TFC score, indicating higher levels in more advanced disease stages (Table 1). After exclusion of participants who had an inflammatory disease, used anti-inflammatory agents, or had hsCRP levels >10 mg/mL (38 time points), effect sizes were not attenuated. No association was found between cytokine levels and disease burden score or TMS.
DISCUSSION

In the present study, in the total group of HD gene expansion carriers, an increase was found TNF-α and IL-10 levels during the 2-year follow-up. This may reflect a reactive elevation of anti-inflammatory cytokines after the initial pro-inflammatory response. IL-6 and IL-8 were inversely associated with the TFC score, whereas no association was found for the other cytokines and measures of disease progression. These findings are only partly in agreement with previous reports in which cytokine levels also correlated with estimated time until onset of disease (derived from the disease burden score) and with TMS (1). Therefore, currently, we cannot decisively conclude that cytokines are useful biomarkers of disease progression in HD.

A limitation of the present study is that we did not control for diurnal variation of cytokine levels. Also, the coefficients of variation were high for IL-1ra, IL-8 and IL-5, thereby increasing the probability of a type II error. Future studies should track cytokine levels in larger populations using multiple assessments in order to verify whether cytokine levels might be markers of disease progression in HD.
REFERENCES


