Chronic fatigue is highly prevalent in survivors of autologous stem cell transplantation and associated with IL-6, neuroticism, cardiorespiratory fitness and obesity

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Running head: Chronic fatigue in lymphoma survivors after HDT-ASCT.

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Chronic fatigue (CF, defined as elevated fatigue levels for ≥6 months) is a common and distressing late effect,[1] affecting 25-30% of long-term lymphoma survivors (LSs),[2,3] compared with 11% in a national representative population.[2] One might hypothesize that CF would be more prevalent after high-dose therapy with autologous stem cell transplantation (HDT-ASCT). However, a prevalence of CF of 28% was found among 40 LSs 3 years after HDT-ASCT, comparable to what is found after conventional chemotherapy.[4]

The etiology of CF in LSs is multifactorial, influenced by demographic, somatic and psychological factors.[1] The underlying pathophysiology is incompletely understood, but is suggested to involve dysregulation of pro-inflammatory cytokines.[1] An association between fatigue and raised levels of cytokines, such as interleukin (IL)-6, IL-1 receptor antagonist (IL-1RA), IL-1β and tumor necrosis factor-α (TNF-α) has been demonstrated, especially in breast cancer survivors.[1] The literature is, however, limited for LSs, with only a few small studies, mainly on mixed hematological diagnoses, that give inconsistent results.[5-7] To our knowledge, no previous study has investigated cytokines in relation to CF in long-term LSs specifically.

On this background, we assessed the prevalence of CF in a national cohort of adult LSs treated with HDT-ASCT, and investigated associations between CF and disease/treatment characteristics, psychological factors and objectively measured somatic variables, including cardiorespiratory fitness and selected cytokines.

All survivors treated with HDT-ASCT for lymphoma in Norway from 1987 to 2008, aged ≥18 years at HDT-ASCT, resident in Norway and not currently undergoing systemic therapy for active malignancy were eligible (n=399), and invited to complete a questionnaire (n=311) and attend a clinical examination (n=270), including echocardiography, symptom-limited cardiopulmonary exercise test, pulmonary function tests and blood samples (supplementary figure S1). For complete methods, see supplementary material.

After a median follow-up of 12 years since diagnosis, the prevalence of CF was 31%. The proportions of chronically fatigued survivors by patient, disease and treatment characteristics and by patient reported outcomes are given in Supplementary Table S1 and by findings on clinical examination in Supplementary Table S2. For LSs having received mediastinal radiotherapy, the prevalence of CF was 39% compared to 27% for those who had not (p=.03). Nineteen percent of survivors meeting the recommendations for physical activity had CF compared with 41% of those who did not (p<.001). Higher scores for neuroticism, post-traumatic symptoms and mental distress were associated with CF (all p<.001).

Thirty-three survivors (12%) were obese, and CF was significantly more frequent among these than among the non-obese (58% vs. 29%, p=.001). The mean peak oxygen consumption (VO_{2peak}) was 24.9 (SD=19) ml/kg/min and 28.0 (SD=7.5) ml/kg/min for survivors with and without CF respectively (p=.003), and corresponding age-, weight- and sex-adjusted expected values were 96% (SD=19%) and 105% (SD=21%) (p=.005). The CF-cases achieved similar exertion as non-CF cases, both objectively (respiratory exchange ratio, p=.72) and perceived (Borg scale, p=.84).

Compared to an age- and gender-matched control group, the LSs had significantly higher levels of IL-1RA (p=.01), higher proportion of detectable IL-6 (p<.001), and lower proportion of detectable IL-1β (p<.001). IL-6 was detectable in 71% of LSs with CF, compared to 51% of LSs without CF (p=.003) and 25% of controls (p<.001) (Supplementary Table S3). Median IL-1RA levels were higher in LSs with CF than in LSs without CF (p=.04) and controls (p<.001).

Logistic regression analysis with CF as dependent variable is shown in table 1. In the multivariable analysis, higher neuroticism score (OR, 1.54; 95%CI, 1.24-1.92, p<.001), obesity (OR, 3.81; 95%CI: 1.49-9.72, p=.005), decreasing VO_{2peak} (OR, 0.45; 95%CI, 0.21-

0.98, p=.01) and detectable serum IL-6 levels (OR, 2.03; 95%CI, 1.03-4.03, p=.04) were associated with increased risk of CF.

In this national cross-sectional study in an unselected cohort of long-term LSs treated with HDT-ASCT, the prevalence of CF was 31%. The prevalence is only slightly higher than in previous studies on LSs after both conventional treatment[2, 3] and HDT-ASCT[4], and considerably higher than in the general Norwegian population,[2] all using the same questionnaire as in the present study.

It has previously been shown that levels of fatigue increase during treatment, decrease in the first year after, and remain stable and above that of the general population at least 3-5 years after treatment.[8] With a median observation time of 12 years, our results suggest that CF is persisting beyond 10 years. The high treatment burden in this group of LSs does, however, not seem to result in much more CF compared to conventional lymphoma treatment. Futhermore, no disease or treatment-related variables were found to be associated with CF in the multivariable analysis.

The majority of studies that until now have shown associations between pro-inflammatory cytokines and CF have been performed among breast cancer survivors.[1] Among LSs, one small study on 30 patients within 3 months of completed chemotherapy found an association between fatigue levels and IL-6,[5] while other studies in different hematological malignancies failed to confirm a relation between cytokine levels and CF.[6, 7] We measured the four cytokines most consistently associated with CF. Both IL-6 and IL-1RA levels were significantly higher in LSs with CF compared with LSs without CF and compared with matched controls from the general population. The association between detectable IL-6 and CF remained significant after adjusting for demographic, treatment, life-style and psychological factors.

Fatigue is a frequent symptom in several diseases characterized by immune activation, including autoimmune diseases and infections.[9] In these processes, and potentially for CF in cancer survivors, fatigue is hypothesized to be due to cytokine signaling in the central nervous system where symptoms of fatigue and other behavioral changes are generated by altering neural processes.[1] Cytokines are important in the pathogenesis of lymphomas, as exemplified by Hodgkin lymphoma where scarce tumor cells are surrounded by reactive immune cells engaged in an abnormal and unproductive immune response. Expression of various cytokines, including IL-6, play an important role in the pathogenesis of lymphomas,[10] and IL-6 levels have been found elevated at diagnosis and associated with B-symptoms and prognosis. Interestingly, we found that IL-6 and IL-1RA levels are increased compared to matched controls from the general population even many years after diagnosis in this population of cancer-free survivors.

Targeting elevated levels of IL-6 by monoclonal antibodies (tociluzumab and siltuximab) represents a therapeutic principle in inflammatory diseases. Recently, Siltuximab was introduced as treatment for multicentric Castlemans disease, a rare lymphoproliferative disorder driven by dysregulated IL-6 production.[11] In the pivotal double-blinded placebo controlled trial, patients reported substantial improvement of fatigue, even in the absence of reduction in other markers of disease activity.[11] This points to the possibility that IL-6 could be a target for pharmacological intervention in cancer survivors with CF in the future. It could be warranted to examine this further in prospective clinical trials.

Lack of physical activity and obesity has previously been shown to be associated with CF.[12] However, this is the first study to assess the possible associations between CF and cardiorespiratory fitness in long-term LSs after HDT-ASCT, showing that VO_{2peak} was significantly lower in survivors with CF. Due to the cross-sectional design we cannot conclude about causality. Physical activity might still be a promising action for CF

intervention, supported by the results from a recent meta-analysis concluding that exercise with or without psychological interventions is effective for reducing CF during and after treatment.[13]

Neuroticism is one of the main personality traits covering degree of emotional instability, and has, in line with our findings, consistently been identified as a strong risk factor for fatigue.[14] However, to the best of our knowledge, associations between neuroticism and CF have not previously been evaluated in LSs.

In accordance with most previous reports, the influence of patient, disease and treatment characteristics on CF seems to be limited.[15] The only treatment related factor we found to be more frequent in survivors with CF was mediastinal radiotherapy, but this did not remain significant in the multivariable analysis.

With detailed and robust information about patient-, disease- and treatment-characteristics, patient-reported psychological, social and life-style factors together with objectively measured somatic health and assessment of potential inflammatory biomarkers, we were able to explore many aspects of the likely multi-factorial mechanisms underlying CF in LSs. This allowed for assessment of, and controlling for, somatic co-morbidities and late effects, some of which have previously been shown to be associated with CF. Neither cardiac disease, pulmonary impairment, endocrine or kidney dysfunction nor anemia was significantly associated with CF.

Despite the limitations inherent in cross-sectional studies, the participation rate in this comprehensive survey was high (78%), and participants and non-participants were highly comparable, strengthening the generalizability of our results. Further, the sample size is reasonably large, and all LSs after HDT-ASCT nationwide are accounted for.

In conclusion, CF is prevalent in this national cohort of long-term LSs after HDT-ASCT, and is independently associated with neuroticism, obesity, poor cardiorespiratory

fitness and detectable serum IL-6. This supports that the etiology of CF is multifactorial, and identify life-style factors that could be targets for prevention and treatment. The results also support immune activation and cytokine dysregulation as a contributing mechanism in the underlying biology of CF, which also could point to possible targets for future interventions.

Competing interests

None declared by the authors.

Supplementary information is available at BMT's website.

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Table 3: Logistic regression analyses

	Univariate			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Female sex (reference male)	1.37	0.83-2.25	.21	0.59	0.22-1.59	.29
Age at survey (years)	0.98	0.96-1.00	.15	0.97	0.94-1.01	.22
Mediastinal radiotherapy	1.81	1.09-3.00	**.02**	1.32	0.63-2.77	.45
Physical activity recommendation met[a]	0.36	0.21-0.60	**<.001**			
Current smoker	1.82	0.99-3.34	.05			
Neuroticism score	1.55	1.34-1.78	**<.001**	1.54	1.24-1.92	**<.001**
Impact of event scale (IES) score	1.04	1.02-1.06	**<.001**	1.01	0.98-1.04	.40
HADS-A	1.20	1.12-1.28	**<.001**			
HADS-D	1.34	1.23-1.46	**<.001**			
Obesity[b]	2.77	1.39-5.50	**.004**	3.81	1.49-9.72	**.005**
VO_2 peak (l/min)	0.60	0.38-0.92	**.02**	0.45	0.21-0.98	**.04**
Work load max (Watt, per 10 units)	0.92	0.86-0.97	**.004**			
IL-6 detectable	2.37	1.34-4.20	**.003**	2.04	1.03-4.03	**.04**
IL-1RA (pg/ml)	1.01	1.00-1.01	**.02**			

Univariate and multivariable logistic regression analyses of potential factors associated with chronic fatigue. Variables with $p \leq 0.10$ in univariate analysis are shown, in addition to age and sex that also were included in the model. [a] 150 min/week of moderate intensity or 75 min/week of vigorous intensity, [b] BMI ≥30. OR = odds ratio, CI = confidence interval, IES = impact of event scale, HADS = hospital anxiety and depression scale (A=anxiety subscale, D=depression subscale), VO_2 = volume oxygen, IL = interleukin. RA = receptor antagonist.