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Chronic Fatigue in Adult Survivors of Childhood Cancer: Associated Symptoms, Neuroendocrine Markers, and Autonomic Cardiovascular Responses

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Background: *Chronic fatigue (CF) is a common late effect after childhood cancer.* **Objective:** *Based on findings among patients with the chronic fatigue syndrome (CFS), this study explored symptoms, neuroendocrine markers, and autonomic cardiovascular responses associated with CFS in childhood cancer survivors.* **Methods:** *Long-term survivors of childhood lymphoma and acute lymphoblastic leukemia reporting CF were compared with survivors without CF. Data included patient-reported outcomes, clinical examination, head-up tilt test, and neuroendocrine markers in the blood and the urine.* **Results:** *Of 102 included survivors, 15 were excluded from comparative analyses because of significant co-morbidity or pregnancy. Of the remaining 87 participants (median age 33.0 years, follow-up time 25.2 years), 35 had CF and 52 did not have CF. Compared with non-CF controls, CF cases reported a significantly ($P < 0.01$) higher frequency of symptoms typical of the CFS (muscle or joint pain or both and feeling confused/disoriented) and symptoms of autonomic dysfunction (palpitations, feeling intermittently heat and cold, and watery diarrhea). CF cases and controls did not differ regarding autonomic cardiovascular responses to orthostatic stress, but the CF group had lower levels of plasma adrenocorticotrophic hormone ($P = 0.002$) and higher levels of urine norepinephrine ($P = 0.017$).* **Conclusions:** *Survivors with CF reported a high symptom-burden compared with controls. There were few differences between both the groups regarding biomarkers, but slight alterations of the hypothalamus-pituitary-adrenal axis and sympathetic nervous activity were detected. CF in cancer survivors has features in common with the CFS, but further efforts are required to clarify the pathophysiology.*

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INTRODUCTION

Chronic fatigue (CF) is a common late effect after cancer therapy,[1–3] not only in cancer affecting adults but also in survivors of childhood cancer.[4–8] Fatigue is a persistent, subjective experience of tiredness and lack of energy, which is not proportional to recent activities and interfers with usual functioning,[2] and it is defined as chronic when it lasts for 6 months or more.[9]

CF in cancer survivors seems to have overlapping clinical features with the chronic fatigue syndrome (CFS).[10,11] CFS is characterized by severe, unexplained,

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long-lasting fatigue accompanied by pain, cognitive impairments, orthostatic intolerance, and other symptoms, resulting in substantial reduction of occupational, educational, social, and personal activities.[9,12] The mechanisms of CFS remain relatively poorly understood. Viral infections,[13] low-grade systemic inflammation,[14] attenuation of the hypothalamus-pituitary-adrenal (HPA) axis,[15] and impairment of executive control functions[16] are reported across adult patients with CFS. Altered autonomic cardiovascular control, eventually causing orthostatic hypotension or tachycardia or both, might also be involved in the pathophysiology.[17–21] The autonomic alterations are characterized by enhanced sympathetic and attenuated parasympathetic cardiovascular nervous activity.[22]

Exploring whether symptoms and pathophysiologic characteristics of CFS apply to cancer survivors with CF may contribute to a better understanding of the latter condition and hopefully to developing preventive and therapeutic strategies. Some of the proposed pathophysiologic mechanisms for CF in cancer survivors are similar to those in CFS, including low-grade inflammation[23] and alterations of the HPA axis.[1] Autonomic alterations might also be a feature of CF in cancer survivors. This hypothesis has not been thoroughly investigated, but a few studies have described symptoms indicating functional autonomic disturbances,[24] altered cardiovascular autonomic responses during orthostatic challenges,[25] and altered neuroendocrine levels in cancer survivors with CF.[24,26]

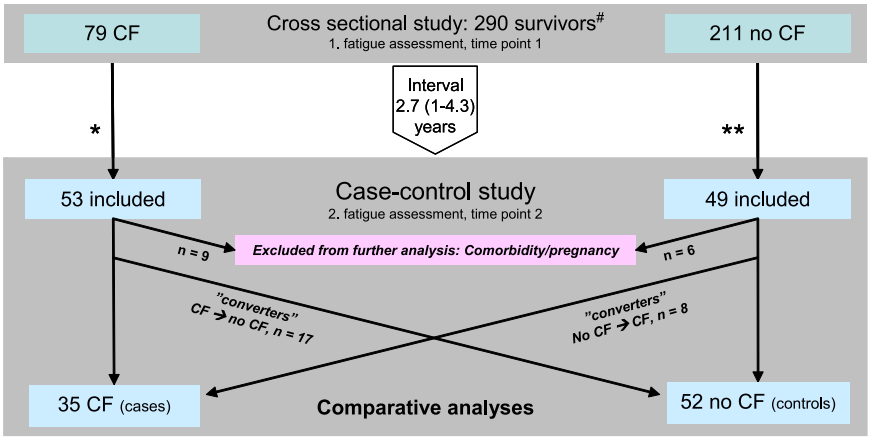
Thus, the aim of this study was to explore if clinical features and pathophysiologic mechanisms reported among patients with CFS are identifiable in adult childhood cancer survivors with CF, particularly focusing on autonomic symptoms, neuroendocrine markers and autonomic cardiovascular responses. Comparing survivors with and without CF, we hypothesized to find similar, but possibly less pronounced, symptom load and biomarker alterations in childhood cancer survivors with CF as reported in patients with CFS.

METHODS

Sample, Inclusion, and Previous Cancer Disease

A flowchart of the study is shown in the Figure. The present study is the second part of a childhood cancer survivorship study including 290 adult survivors of childhood acute lymphoblastic leukemia (ALL) or lymphoma.[4] Inclusion criteria in the first part were treatment at Oslo University Hospital (ALL) or whole of Norway (lymphomas), diagnosis between 1970 and 2002 at age $\leq$16 years (ALL) or $\leq$18 years (lymphoma), and at least 5 years observation time from diagnosis. In the present study (time point 2, TP2), survivors reporting CF in the original study (time

FIGURE. Study Flowchart. CF: Chronic Fatigue.



For inclusion criteria, see methods section
* 1 survivor excluded due to severe somatic disease/immobility. 78 invited to participate. 56 willing to participate. 3 not investigated.
** 130 invited to participate (matched with regard to diagnosis, otherwise randomly). 67 willing to participate (3 of these excluded due to ongoing pregnancies), 15 not investigated.