EUROPEAN JOURNAL OF CANCER 43 (2007) 2685–2690

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Orthostatic intolerance in survivors of childhood cancer

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ARTICLE INFO

Article history:
Received 11 February 2007
Received in revised form 21 June 2007
Accepted 27 June 2007
Available online 8 August 2007

Keywords:
Orthostatic intolerance
Cancer survivors
Fatigue
Neurally mediated hypotension (NMH)
Postural orthostatic tachycardia syndrome (POTS)

ABSTRACT

Purpose: To compare the prevalence and severity of orthostatic intolerance in survivors of childhood cancer and in healthy controls, and to correlate results of self-reported measures of health status with orthostatic testing in survivors of childhood cancer.
Patient and methods: Thirty-nine survivors of childhood cancer and 56 controls were recruited for this study. Each cancer survivor completed standardised self-report measures and all participants underwent a standing test (5 min supine, 10 min of motionless standing leaning against a wall, followed by another 2 min supine). The main outcomes of the standing test were orthostatic tachycardia (OT), defined as a heart rate increase of at least 30 beats per minute (bpm) during standing, and neurally mediated hypotension (NMH), defined as a drop in systolic blood pressure of at least 25 mm Hg.
Results: OT developed in 22/39 (56%) cancer survivors versus 17/56 (30%) controls ($P = .01$). Cancer survivors had a higher baseline and maximum standing heart rate (both $P < .001$) and a more rapid onset of significant OT ($P = .005$). No significant difference in scores on self-report measures was found between cancer survivors with or without OT.
Conclusion: This study provides preliminary evidence of a higher rate of orthostatic intolerance in childhood cancer survivors. Further study is warranted to better define whether this is a modifiable risk factor for fatigue in this population, and how orthostatic intolerance interacts with other known risk factors for lowered quality of life.

1. Introduction

Fatigue has emerged as a common and distressing symptom experienced by survivors of childhood cancer[1–4] and is one of the most important determinants of quality of life for the cancer survivor.[5] A substantial overlap is seen between the clinical characteristics and impact of fatigue in cancer survivors and in patients with chronic fatigue syndrome (CFS).[6,7] Fatigue is a multidimensional experience that involves physical, mental, emotional, environmental, physiological and pathological aspects. Due in part to this complexity, fatigue remains a poorly understood phenomenon. Because treatment approaches for fatigue are limited, identifying potentially modifiable risk factors for fatigue is important.

Our group has been interested in the contribution of circulatory dysfunction to chronic fatigue. Several cross-sectional studies have shown that constitutional hypotension is associated with a greater prevalence of fatigue.[8–11] In one cohort study, constitutional hypotension was a risk factor for later

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doi:10.1016/j.ejca.2007.06.017

development of idiopathic chronic fatigue in females.[12] Moreover, individuals with the most extreme forms of hypotension, such as orthostatic hypotension, frequently report chronic fatigue.[13,14] Two forms of orthostatic intolerance have been found to be prevalent in patients with chronic fatigue syndrome: neurally mediated hypotension (NMH) and postural orthostatic tachycardia syndrome (POTS).[15–20] In non-blinded treatment studies, CFS symptoms have been shown to improve after treatment of orthostatic intolerance.[15,16]

NMH is a common disturbance of blood pressure control often referred to as delayed orthostatic hypotension, neurocardiogenic syncope, vasovagal syncope or vasodepressor syncope.[21–23] NMH is defined as a drop in systolic blood pressure of $\geqslant$25 mm Hg from baseline supine measurement during prolonged orthostatic challenge, associated with provocation of typical symptoms.[20] In individuals with NMH, blood pressure falls as a consequence of abnormal activation of a neurocardiogenic reflex. The reflex is initiated when left ventricular volume is reduced, usually from excessive dependent pooling of blood after prolonged sitting or standing (because of a failure to mobilise blood effectively from the splanchnic and limb vasculature)[23–26] and usually associated with an increase in catecholamine secretion.[27,28]

POTS is a related and pathophysiologically heterogeneous form of circulatory dysfunction,[29–32] defined by a heart rate increase of at least 30 beats per minute (bpm), or an absolute heart rate of $\geqslant$120 bpm during the first ten minutes of upright tilt or standing, associated with reproduction of orthostatic symptoms.[32] As in NMH there appears to be a failure to mobilise blood effectively from the dependent splanchnic and limb vasculature when affected individuals are upright.[33,34] Subgroups with POTS have been defined with elevations in plasma norepinephrine, low blood volume and autoantibodies.[31] Some individuals with tachycardia during the first 10 min of upright posture can develop NMH with more prolonged standing.[20]

Symptoms frequently reported by those with NMH and POTS include lightheadedness, fatigue, exercise intolerance, epigastric discomfort, nausea, pallor, a sense of hearing voices distantly, diminished concentration, headache, tremulousness, diaphoresis, hyperpnea, blurred vision, and in some, syncope.[23,30,31,35] Precipitating factors associated with development of NMH and POTS are those which either reduce ventricular filling or increase catecholamine secretion, including prolonged quiet sitting or standing, exercise, emotional stress and exposure to warm environments.

Cancer survivors may be at risk for orthostatic intolerance because of the known autonomic effects of chemotherapy and radiation therapy,[36] together with the relative hypovolemia that would be expected to accompany nausea, dehydration, and prolonged bed rest during cancer treatment. In response to orthostatic symptoms caused by such hypovolemia, individuals who choose to rest might be predisposed to persistent hypovolemia and thus to chronic orthostatic intolerance. Based on the overlap of cancer-related fatigue and chronic fatigue syndrome, and on the overlap between chronic fatigue syndrome and orthostatic intolerance syndromes, we hypothesised that orthostatic intolerance would contribute to the symptoms of fatigue and impaired quality of life seen in some cancer survivors.

The purposes of this study were to compare the prevalence and severity of orthostatic intolerance in survivors of childhood cancer and in a group of healthy controls, and to assess whether self-reported measures of fatigue and quality of life correlated with measures of orthostatic tolerance.

2. Patient and methods

2.1. Recruitment cases and controls

This study combined a pilot and follow-up investigation performed in the Long-Term Follow-Up clinic at the Johns Hopkins Oncology Center. Patients seen in clinic were eligible for the study if they met the following criteria: age <18 at the time of cancer diagnosis, age >12 years at the time of the study, at least 6 months off cancer therapy, no other serious, confounding medical conditions currently requiring therapy, not currently being treated for a psychiatric or emotional illness, and with a Beck Depression Inventory score less than 16.

Healthy controls were recruited from the Baltimore area by means of advertisements posted on bulletin boards at the Johns Hopkins University. All studies were approved by the Institutional Review Board of the Johns Hopkins Hospital. All subjects provided informed consent.

Cases and controls were excluded if they had taken the following in the two weeks before the standing test: antidepressants, diuretics, mineralocorticoids or glucocorticoids, or drugs known to interfere with results of orthostatic testing (e.g. beta-adrenergic antagonists, vasoconstrictor medications, selective serotonin re-uptake inhibitors, fludrocortisone).[20,23] Like cases, controls were excluded if they had a serious acute or chronic medical or psychiatric condition.

2.2. Measures of health status

Participating cancer survivors completed the following self-report measures:

(1) *Medical Outcomes Study 36-item Short Form Health Survey (SF-36)*: This questionnaire examines physical functioning, role limitations because of physical health, bodily pain, social functioning, general mental health, role limitations because of emotional problems, vitality and general health perceptions. The SF-36 is scored on a scale of 0–100, higher scores indicating better function.[37]

(2) *Beck Depression Inventory (BDI)*: This self-administered scale of depression is valid, reliable, and has been used in depression research since 1961.[38] We regarded a Beck score of 16 or more as an indication of possible depression, and excluded those with scores in this range.

(3) *Wood Mental Fatigue Inventory (WMFI)*: This questionnaire asks subjects to rate nine mental fatigue symptoms (spells of confusion, thoughts getting mixed up, poor concentration, cannot easily make decisions, poor memory for recent events, cannot take things in when speaking to people, thoughts are slow, muzzy or foggy head, cannot find the right words).[39] Responses are scored as follows: 'not at all' (0 points), 'a little' (1), 'somewhat' (2), 'quite a lot' (3) and 'very much' (4).

2.3. Orthostatic testing

Orthostatic tolerance was assessed using a brief standing test. This test began with 5 min supine. The baseline heart rate (HR) and blood pressure (BP) were measured at the 4th and 5th minute supine, and the mean of these two measurements formed the baseline supine hemodynamic values. The patient was then instructed to stand with feet 3–12 in. away from the wall, in a comfortable but motionless stance for a maximum of 10 min. The patient then returned to the supine position for 2 min. Heart rate and blood pressure were recorded with an automated blood pressure cuff; the study personnel were not blinded to the case or control status of the subjects. The test was performed in a quiet room and was stopped at the request of the participant, or if the participant developed presyncopal symptoms or syncope.

An abnormal standing test was defined as a heart rate increase from the supine baseline of at least 30 bpm within 10 min upright or a heart rate of $\geqslant$120 bpm during standing (orthostatic tachycardia, OT), or as at least a 25 mmHg decrease in systolic blood pressure from baseline supine values, with no associated increase in heart rate (NMH), or as the emergence of presyncopal symptoms. Symptoms were not recorded systematically during the standing test for the cancer survivors.

2.4. Statistical analysis

We examined the data on heart rate and blood pressure first by comparing all cases to controls. Because of differences between males and females with regard to blood pressure and heart rate in response to orthostatic challenge, we also compared the hemodynamic data independently by gender.[40,41] Continuous data were compared using independent-samples T tests when the data were normally distributed. Categorical variables were compared using the χ^2 statistic or the Fisher's exact test. Differences between cases and controls in the time until the heart rate increased 30 beats per minute during standing were compared with Kaplan–Meier curves using the Log rank statistic. All P-values presented are two-sided and a P-value of less than .05 was considered significant. Data were analysed using SPSS statistical software (Version 14.0).

3. Results

3.1. Study participants

Of 41 childhood cancer survivors who were screened for participation, 2 were excluded due to a Beck score $\geqslant$16, leaving 39 eligible for the study. Of the 69 controls, 13 were excluded due to medications or other medical conditions, leaving a final sample of 56 controls (35 male, 21 female; 33 White, 3 Black, 16 Asian, 2 Hispanic, 4 of other races). The demographic characteristics of the cancer survivors are listed in Table 1. Sixteen were male and 23 female; mean age was 19.3 (range 12–42 years) at the time of study, 32 were White and 7 were Black. The most common diagnoses were Hodgkin lymphoma (33%), acute lymphoblastic leukaemia (23%) and Wilm's tumour (15%). Cancer survivors were younger than controls at the time of study (19.3 ± 6.8 versus 23.2 ± 4.8 years; $P < .01$).

Table 1 – Characteristics of childhood cancer survivors

Variables	Cancer survivors (n = 39)
Demographics	
Gender	23 female, 16 male
Age at study	19.3 ± 6.8[a], range 12–42 years
Age at diagnosis	9.4 ± 5.8, range 0.1–17 years
Years off therapy	8.8 ± 7.3, range 1–38 years
Clinical diagnoses	
Hodgkin lymphoma	13 (33%)
Acute lymphoblastic leukaemia	9 (23%)
Wilm's tumour	6 (15%)
Neuroblastoma	2 (5%)
Non-Hodgkin lymphoma	2 (5%)
Acute myeloid leukaemia	2 (5%)
Chronic myeloid leukaemia	1 (3%)
Germ cell tumour	1 (3%)
Rhabdomyosarcoma	1 (3%)
Ewings sarcoma	1 (3%)
Burkitt lymphoma	1 (3%)
Prior therapies	
Vincristine	28 (72%)
Doxorubicin	22 (56%)
Bleomycin	11 (28%)
Mantle radiation	19 (49%)
Bone marrow transplant	5 (13%)
Quality of Life Measures	
Beck Depression Inventory	4.2 ± 4.2, range 0–14
Wood Mental Fatigue Inventory	4.4 ± 5.0, range 0–17
SF-36 physical health summary score	51.5 ± 7.7, range 27.3–64
SF-36 mental health summary score	50.7 ± 9.6, range 19.9–63

a Unless otherwise noted, values represent mean ± SD.

3.2. Baseline supine measures

For the study population as a whole, baseline systolic blood pressure did not differ between cancer survivors and controls, but cancer survivors had lower diastolic blood pressures and higher baseline heart rates (Table 2). Among males, cancer survivors showed a higher heart rate in the supine position than controls ($P = .01$). The baseline diastolic blood pressure among female cancer survivors was lower ($P = .04$).

3.3. Hemodynamic responses to standing test

For the study population as a whole, orthostatic tachycardia developed in 22/39 cancer survivors (56%) and in 17/56 (30%) controls ($P = .01$). Peak heart rate was higher in cancer survivors compared to controls overall ($P < .001$), and these differences remained after comparing the groups by gender (both $P < .01$; Table 2). The median time to a heart rate increase of $\geqslant$30 bpm was shorter in cancer survivors than in controls overall (6 versus 10 min; $P = .005$, Log-rank test) (Fig. 1). After comparing the groups by gender, the difference in time to OT remained significant in males ($P < .05$) but not in females

Table 2 – Characteristics and test results, childhood cancer survivors and controls

Variables	Cancer survivors (n = 39)	Controls (n = 56)	P	Female cancer survivors (n = 23)	Female controls (n = 21)	P	Male cancer survivors (n = 16)	Male controls (n = 35)	P
Age at study	19.3 ± 6.8	23.2 ± 4.8	<.01	19.9 ± 6.6	23.4 ± 5.7	.07	18.4 ± 7.2	23.0 ± 4.4	<.01
Baseline SBP	113 ± 10	114 ± 12	.56	110 ± 9	110 ± 11	.81	116 ± 10	117 ± 12	.85
Baseline DBP	60 ± 9	64 ± 7	.02	60 ± 9	65 ± 8	.04	59 ± 10	63 ± 6	.11
Baseline HR	69 ± 11	61 ± 10	<.001	73 ± 10	67 ± 11	.06	64 ± 10	57 ± 7	<.01
Peak HR	102 ± 14	87 ± 16	<.001	106 ± 14	94 ± 15	<.01	97 ± 13	84 ± 16	<.01
Lowest HR supine	65 ± 11	59 ± 9	<.01	68 ± 10	64 ± 11	.23	61 ± 12	55 ± 7	.02
HR change baseline to maximum	33 ± 10	27 ± 10	<.01	33 ± 12	27 ± 9	.07	32 ± 8	27 ± 11	.07

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute. Mean ± SD.

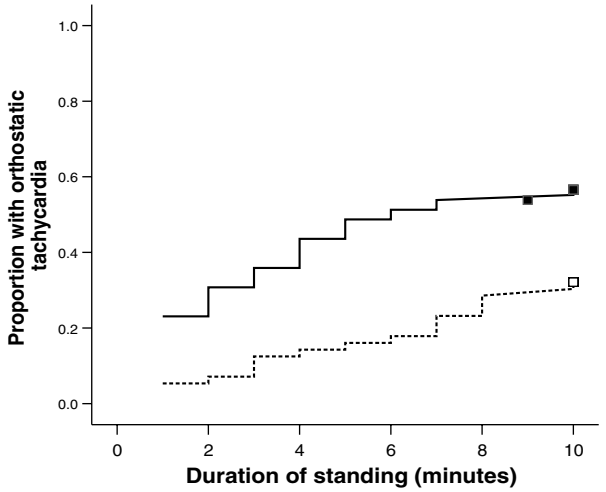

Fig. 1 – Kaplan–Meier analysis of the probability of orthostatic tachycardia during 10 min of standing. Cancer survivors (solid line) were more likely to develop orthostatic tachycardia (defined as a HR increase of ⩾30 bpm) than controls (dashed line), (P = .005, Log-rank test). Squares indicate censored subjects.

(P = .17). Among females, OT developed in 13/23 (57%) cancer survivors compared to 8/21 (38%) controls (P = .25). Among males, 9/16 (56%) cancer survivors developed OT versus 9/35 (26%) controls (P = .06). Among those with OT in each group, one female cancer survivor and two male controls also had NMH.

3.4. *Correlations with OT*

No definitive association could be made between the presence of OT and cancer type, or with cancer treatment using vincristine, bleomycin, doxorubicin, or mantle radiation. All five bone marrow transplant patients studied demonstrated OT, but this difference did not reach statistical significance when compared to those who had not undergone bone marrow transplant (P = .06). Cancer survivors with and without OT did not differ significantly on the Beck, Wood, or summary scores of the SF-36. None of eight subtests of the SF-36 differed between groups.

4. Discussion

This study identified a significantly higher prevalence of circulatory abnormalities in cancer survivors compared to controls. Cancer survivors had higher baseline heart rates, higher peak heart rates during 10 min of standing, and a more rapid onset of significant orthostatic tachycardia (defined as an increase of ⩾30 bpm). We believe these data might underestimate the prevalence of circulatory abnormalities in our study population, because our brief 10 min test of orthostatic tolerance would not have been long enough to identify most instances of neurally mediated hypotension. The latter is usually diagnosed during a 45–60 min upright tilt table test.

The clinical importance of this higher prevalence of orthostatic tachycardia will need to be explored further. Our data did not identify an association between scores on self-reported measures of health status and measures of heart rate and blood pressure during standing. There may be several reasons for this finding. First, it is possible that there is no contribution of orthostatic intolerance to diminished well-being in the cancer survivor. This seems unlikely given what is known about the impact of similar degrees of orthostatic intolerance in other populations.[42,43] Second, our sample size may not have been adequate to identify the relative contributions of OT to health impairment, given that determinants of fatigue and impaired health in cancer survivors are likely heterogeneous. Third, assessing symptoms of fatigue in the young cancer survivor by self-report measures is difficult, because childhood cancer survivors are more likely to give an overly positive self-assessment about their health compared to the normal population.[44,45] We were surprised that cancer survivors rated their physical health summary scores higher than the mean reported for the United States (US) population (51.5 ± 7.7 versus 50.0 ± 10.0).[37] Self-assessment by standard questionnaires may be flawed in the cancer survivor population, because improvement in well-being in comparison to the treatment period (in some cases, much of childhood) leads to a different baseline for self-evaluation than in the normal population. Fourth, the measures of fatigue in this study (the subscales of the SF-36, the Wood mental Fatigue Inventory) did not encompass all dimensions of fatigue. Future studies of this issue will need to use more comprehen-

sive instruments such as the Multidimensional Assessment of Fatigue,[46] the Multidimensional Fatigue Inventory,[47] or other measures (discussed in Ref. [48]). Finally, prospective treatment trials may be needed for further exploration of the hypothesis that treating orthostatic intolerance will improve quality of life.

We would emphasise that this study has several limitations. First, its sample size is relatively small. This interfered with a more complete examination of the role of hemodynamic data by gender, although trends in heart rate response were similar for gender subgroups. Similarly, the age of the cancer survivors at the time of study was lower than the controls, although this statistical difference is not likely to have exerted a strong physiologic or clinical effect. We were unable to further evaluate whether different cancer diagnoses or specific cancer therapies such as chemotherapy or radiation were associated with an increased risk of orthostatic intolerance. The association with bone marrow transplant approached significance, but the number of patients who had been transplanted was small.

We would also caution that our sample may not be representative of all long-term survivors. We enrolled a sample of clinic patients who participated in the long-term follow-up programme; we did not have a systematic sample of cancer survivors. We do not know how subjects in a long-term follow-up programme compare to the general population of cancer survivors, but it is reasonable to assume that these patients have more complications than the general cancer survivor population.

Moreover, participants in this study were excluded if they had high scores on the Beck Depression Inventory, so our results should not be extrapolated to populations with a heavier burden of depression. We do not know the rates of orthostatic intolerance in cancer survivors with depression. No large studies have looked at the interaction of depression and circulatory dysfunction during orthostatic challenge, but cross-sectional studies have reported an association between constitutional low blood pressure and depression.[10,11] Whether there is a relationship between depression and orthostatic intolerance and if they both contribute to the fatigue seen in cancer survivors is also an area for further investigation.

Our data do not define a true prevalence of OI in the general population of cancer survivors, but they provide preliminary evidence that circulatory disorders may be more common than had been suspected. Because orthostatic tachycardia and hypotension can be treated with both nonpharmacologic measures and medications,[16,23,32] further study is warranted to better define whether regimens directed at these circulatory dysfunctions can improve symptoms and quality of life in cancer survivors with orthostatic intolerance.

Conflict of Interest Statement

None of the authors (Annelinde Terlou, Kathy Ruble, CPNP, Anne F. Stapert, Ho-Choong Chang, MD, Peter C. Rowe, MD, Cindy L. Schwartz, MD) has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the paper entitled 'Orthostatic intolerance in survivors of childhood cancer'.

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