chapter 5

Persisting fatigue in Hodgkin lymphoma survivors: A systematic review

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Abstract

Purpose
Hodgkin lymphoma (HL) survivors are at risk for adverse psychosocial events as a result from cancer diagnosis and treatment. Fatigue is one of the most frequently reported long-term symptoms and is often reported to interfere with daily life. We conducted a systematic review to determine prevalence, severity and predisposing factors of fatigue in HL survivors.

Methods
A literature search was conducted up to August 2012. Twenty-two articles comparing HL survivors with norm population data met all predefined selection criteria. Prevalence rates, levels of fatigue and clinical relevance of the results were determined.

Results
Prevalence of fatigue ranged from 11%-76% in HL survivors compared with 10% in the general population. Mean fatigue scores were 5-13% higher compared with the normative population; these findings were clinically relevant in 7 out of 11 studies. Increasing age was associated with higher levels of fatigue in HL survivors. Treatment modality and stage of initial disease were not associated with higher fatigue levels, while comorbidities or other treatment sequelae seemed to impact on the levels of fatigue.

Conclusions
HL survivors are at serious risk for developing clinically relevant, long-term fatigue. The impact of patient- and treatment characteristics on risk of fatigue is limited. Focus for future research should shift to the role of late-treatment sequelae and psychological distress symptoms.

Introduction

Hodgkin lymphoma (HL) is a relatively rare form of cancer. HL mainly affects adolescents and young adults. Significant therapeutic improvements have resulted nowadays in a favorable prognosis with an overall 5-year cancer-specific survival rate of 80% (1). The combination of highest incidence at a young age and improved survival has, however, led to an increasing number of HL survivors, who remain at risk for long-term complications of their treatment. Many studies have focused on adverse physical effects of treatment, such as an increased risk of secondary tumors (2, 3) or cardiovascular events (4, 5). Since the 1990s, studies have increasingly been focused on psychosomatic and psychosocial aspects of treatment and on the burden of having survived cancer. Fatigue is one of the most frequently reported symptoms among (long-term) survivors of HL (6-9). It is a main component of the multidimensional concept of health-related quality of life (HRQL). Fatigue and associated symptoms such as lack of energy or loss of vitality are among the symptoms rated most often as interfering with daily life. It has been reported to have a significant impact on perceived HRQL, even more so than some specific physical symptoms like nausea or pain (10). Fatigue itself has therefore been addressed in several studies, either briefly when measuring general HRQL in HL survivors, or more explicitly in studies using specifically designed and validated fatigue questionnaires. Most of these articles have also investigated the relation of fatigue with patient- and treatment-related factors. Since many of these studies were cross-sectional by design, their findings merely give an indication of possible associations, and their findings were often contradictory.

The purpose of this review was to provide a comprehensive overview of studies which have investigated fatigue in HL survivors, focusing on the prevalence and severity of fatigue and on associations between patient- and treatment-related factors and levels of fatigue.

Methods

Literature search strategy

A literature search was performed for all articles up to August 2012 using the electronic databases of Web of Science, PubMed en PsychINFO. Key terms used in the search were 'Hodgkin', 'Hodgkin's' and 'Hodgkins' in combination with '(Health related) Quality of Life', 'Value of Life', 'Fatigue', 'Energy Level' or 'Vitality'. Lists of references were verified to find additional publications that were not found by the computerized search.

Selection criteria

The literature search resulted in 1975 hits, of which 432 were duplicates. A total of 1395 were excluded based on title. Of the 148 abstracts retrieved, 52 were selected for full text review. Selection of articles was based on English language and measurement of fatigue by generic and/or fatigue-specific questionnaires. Abstracts, studies conducted before 1990, studies combining results of more than one type of tumor, or addressing fatigue in a specific subgroup of patients such as those who had intensified treatment for relapsed or refractory HL, were excluded. Subject of the studies had to be either comparison of fatigue in HL survivors with a well-defined norm population, and/or analysis of the relationship of fatigue with patient- and treatment characteristics. Specific focus was placed on the relationship between late-treatment sequelae or comorbid conditions and fatigue.

A total of 28 articles met the described selection. Six (11-16) review articles were further excluded since they only briefly discussed fatigue, and did not contain any additional studies to the remaining 22 original articles.

Quality assessment

The methodological quality of the selected articles was defined by scoring items from a standardized checklist with predefined criteria. These criteria originated from an established criteria list for systematic reviews that was previously used (16-18) which was slightly adapted for the purpose of this review. The criteria are listed in Table 5.1. For every one of the criteria that was met, one point was assigned to the study. In case of absence of an item, zero points were assigned. Therefore, a total number ranging from 0 to 14 points per study was assigned to each study. A higher total score indicates a higher quality assessment. Studies scoring 75% ($\geq$11 points) or more were considered as 'high quality studies'. A score between 50% and 75% was considered to be moderate and studies scoring less than 50% were qualified as 'low quality'.

The evaluation of the methodological quality of studies was done separately by LAD and SO. A consensus meeting was held to discuss differences between the two reviewers and a consensus score was assigned.

To determine clinical relevance of reported differences in mean fatigue scores for studies comparing HL survivors to a norm or control group we used the following guidelines. For the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) differences were defined according to the EORTC guidelines as trivial (0-5 point difference), small (5-13 point difference) or medium (13-19 point difference) (19). Concerning the Short Form-36 (SF-36) $\geq$ 3

Table 5.1: Criteria for assessing the methodological quality of studies of fatigue in HL survivors*

Quality of life assessment	
1.	a validated fatigue specific or generic HRQL questionnaire measuring fatigue or vitality is used (*e.g.* FQ, SF-36, EORTC QLQ-C30)
Study population	
2.	a description is given of at least two socio-demographic variables
3.	a description is given of at least two clinical variables
4.	in- and exclusion criteria are described
5.	response rate to the QoL or fatigue questionnaire is $\geq$ 65%
6.	information is provided on differences of characteristics between responders and non-responders
7.	time since diagnosis is provided
Study design	
8.	the study size consist of at least 50 participants
9.	data are prospectively gathered
10.	the process of data collection is described
11.	missing data are described
Results	
12.	the results are compared between two groups or more (*e.g.* healthy population, groups with different treatment or age and/or compared with at least two time points)
13.	mean, median, standard deviations or percentages are reported for the most important clinical outcome measure
14.	statistical proof for the findings is reported

* adapted from (16-18).

Abbreviations: HRQL = health-related quality of life; FQ = Fatigue questionnaire; SF-36 = short form 36; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire.

points difference was considered clinically relevant (20). For the other questionnaires, Norman's 'rule of thumb' was used, whereas a difference of $>$ 0.5 SD indicates a discriminating change in fatigue scores (21).

Results

Study characteristics

All 22 identified studies had been published between 1993 and 2013. Seven studies focused specifically on fatigue (22-28); while in the other 15 fatigue was measured and reported as part of the assessment of HRQL (8, 9, 29-41).

Two studies had a prospective, longitudinal design (8, 39). Both of these studies were HRQL protocols associated with large multicentre clinical randomized trials, comparing different treatment strategies. Eighteen studies had a cross-sectional design, either in a single center (23, 25-27, 29, 30, 33, 35-38, 40, 41) or multicenter setting (9, 24, 31, 32, 34). Two studies were follow-up studies of earlier cross-sectional reports (22, 28).

In 12 of the 18 cross-sectional studies, HL survivor fatigue levels were compared with data from a general norm population (22, 24, 25, 29-31, 34, 37) or to matched cases (9, 23, 35, 36). The remaining six described fatigue within a HL survivor cohort and were selected because they explored associations between fatigue and patient- or treatment parameters. The total number of patients included in all studies ranged from 42 (41) to 935 (39), and median time since diagnosis ranged from 6 months (8) to 24 years (28).

Of all 22 studies, 16 reported on associations of clinical and/or treatment characteristics with higher levels of fatigue (8, 9, 22-27, 29-31, 35, 38-41).

The validated questionnaires that were used in the studies either measured fatigue specifically (Fatigue questionnaire (FQ) (42), Multidimensional Fatigue Inventory (43)), (22, 24, 25, 29, 39), or measured fatigue as a scale of a generic or cancer-specific HRQL questionnaire (Short Form 36 (SF-36) (44), EORTC QLQ-C30 (45)), (8, 23, 24, 28, 30, 31, 34-39, 41). The SF-36 addresses fatigue and energy by measuring a four-item vitality scale, the EORTC QLQ-C30 measures a separate three-item fatigue scale. Questionnaires less often used were the Profile of Mood States (POMS(46)), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F (47)) and the Schedule for the Evaluation of Individual QoL-Direct Weighting (SeisQoL-DW (48)), each used in one study (9,23, 32).

Prevalence of fatigue

Seven studies reported prevalence rates of fatigue, ranging between 11% and 76% (see Tables 5.2 and 5.3). However, five of these seven studies reported on the same Norwegian HL survivor cohort, measured at two time intervals. As a result, they reported similar fatigue prevalence rates, defined as a dichotomized score of 4 out of 11 questions in the FQ, of 26% (measured in 1994, (25-27)) and 30% (measured in 2002, (29, 33)). Rates of fatigue in the HL survivor cohort (26-30%) in these five studies were significantly higher than the 10% fatigue that was measured in the population survey (25, 29, 49).

Two studies reported on other cohorts of HL survivors. One (40) reported a prevalence of at least some level of fatigue in 76% of 168 HL survivors, using a score of $\geq$ 20 out of a possible 100 in the EORTC QLQ-C30 as cut-off. The other (32) found that 11% of 121 HL survivors self-indicated fatigue as an area importantly affected by HL diagnosis and treatment.

Fatigue scores

Sixteen studies reported mean fatigue scores in HL survivors (see Tables 5.2 and 5.3). Among the 12 studies that compared mean fatigue scores to a norm population or a set of matched cases, the two smallest case-control studies did not find significant differences in levels of fatigue (35, 36). The remaining 10 studies all showed statistically significant higher fatigue scores in HL survivors compared with norm data (9, 22-25, 29-31, 34, 37). Only two of these studies addressed the clinical relevance of higher fatigue scores in HL survivors by reporting effect size. Hjermstad *et al.* (29) reported an effect size of 0.7 measured by FQ, which was defined as moderate, and Loge *et al.* reported a small effect size of 0.23 measured by SF-36 (30). Overall, differences in fatigue scores between HL survivors and normative populations ranged from 5-13%. Three studies used the EORTC QLQ-C30 questionnaire, of which two measured a difference of 6.5 points (6.5%), compared with the general population (24, 34). Brandt *et al.* (37) found a difference of 13 points (13%) in fatigue scores on the QLQ-C30 between HL patients treated with chemotherapy alone, and a German reference population. Two studies reported on vitality scores using the SF-36, and found differences of 5% and 8%, respectively (30, 31). Three studies used the FQ for assessment of fatigue. All of these studied the same HL cohort (at two different time intervals) and used a general practitioner survey for norm data, and reported differences in fatigue scores of 6-7% (22, 25, 29).

The two prospective, longitudinal studies evaluating fatigue in HL trial cohorts (8,

Table 5.2: Overview of studies of fatigue in HL survivors without comparison to normative data

Study, year	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm popu-lation	Fatigue outcome	Major findings	Quality Score
Ganz (8) 2003	247	33 (17-85)	0.5, 1 and 2	RT or CMT	Longitudinal prospective	98-70%	SF-36	No	Increase of fatigue first 6 months after treatment, returning to baseline level at one year after diagnosis	Fatigue more severe after CMT, both treatment arms return to baseline level of fatigue	14
Heutte (39) 2009	935	NR (15-70)	7.5 (4.3-9.8)	RT or CMT	Longitudinal prospective	74-32%	EORTC QLQ-C30 MFI	No	Improvement of fatigue up to two years after treatment in 65% of patients, no baseline reports.	Increasing fatigue with age. Fatigue at end of treatment only predictor for persistent fatigue	14
Loge (26) 2000 *	421	NR	3-23	RT, CT or CMT	Cross-sectional	92%	FQ	No	Prevalence of fatigue 26%mean fatigue score not reported	Higher fatigue levels with age and lower educational level. No differences between: stage, gender, treatment or time since diagnosis	13
Knobel (27) 2001 *	92	37 (30-43)	9 (6-12)	RT or CMT	Cross-sectional	n.a.	FQ	No	Mean fatigue score 15, physical 10, mental 5. Prevalence of fatigue 26%	More fatigue in patients with pulmonary dysfunction. No association with cardiac or thyroid disease or patient and treatment characteristics	12
Norum (41) 1996	42	NR	4.3 (16-120)	RT, CT or CMT	Cross-sectional	86%	EORTC QLQ-C30	No	Mean fatigue score 28.6	Higher fatigue scores in menNo differences between treatment	11
Ng (27) 2013	422	52 (31-78)	24 (14-43)	RT, CT or CMT	FU on cross-sectional study	65%	FACIT-FSF-36	No	Overall no significant difference in fatigue scores compared with earlier	Significant increase of fatigue in patients suffering from cardiac or pulmonary complications	11
Greill (38) 1999	126	NR	9.1 SD ± 7.0	RT, CT or CMT	Cross-sectional	65%	EORTC QLQ-C30	No	Mean fatigue score not reported	More fatigue after CMT versus CT or RT alone	10
Miltenyi (40) 2010	168	43 (18-77)	9.5 (0-36)	RT, CT or CMT	Cross-sectional	NR	EORTC QLQ-C30	No	Any form of fatigue 76%	More fatigue in patients suffering from late complications and those more than 20 years after treatmentNo differences between stage, treatment, gender, B-symptoms	9

Abbreviations: HL = Hodgkin lymphoma; n.a: .not applicable; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; SF-36 = short-form 36; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MFI= Multidimensional Fatigue Inventory; FQ= fatigue questionnaire.

* Studies reporting results from the same HL survivor cohort. NR: not reported.

Table 5.3: Overview of studies on fatigue in HL survivors with comparison to normative data

Study	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm population	Fatigue outcome	Major findings	Clinically relevant difference	Quality Score
Hjermstad (22) 2005 *	476	46 (21-74)	16 (4.4-36)	RT, CT or CMT	FU on cross-sectional study	81%	FQ	Yes, comparison to age, sex and education adjusted GP survey	Moderately higher total fatigue in HL survivors	Increasing fatigue with age. Increased persisting fatigue in patients presenting with B-symptoms	No	13
Hjermstad (29) 2006 *	476	46 (21-74)	16 (4.4-36)	RT, CT or CMT	Cross-sectional	81%	SF-36 FQ	Yes, comparison to age, sex and education adjusted GP survey	3 times more chronic fatigue HL survivors than norm population (30% vs 11%)	No differences between: time since diagnosis, stage, treatment (intensity), B-symptoms	No	13
Loge (30) 1999 *	459	44 (40-49)	12.2 (3 -23)	RT, CT or CMT	Cross-sectional	82%	SF-36	Yes, comparison representative sample of Norwegian population (N=3500)	Vitality significantly lower in HL survivors	No significant differences in fatigue between treatment, stage, relapse, time since diagnosis	Yes	13
Loge (25) 1999 (JCO) *	459	44 (40-49)	12.2 (3-23)	RT, CT or CMT	Cross-sectional	82%	FQ	Yes, comparison representative sample of Norwegian population (N=3500)	Prevalence of fatigue 26% vs 11%, higher fatigue scores in HL survivors	Higher fatigue with age and low educational level. No differences between: stage, treatment, time since diagnosis, gender	-	13
Mols (31) 2006	132	NR	5- 15	RT, CT or CMT	Cross-sectional	80%	SF-36, QLQ-CS	Yes, comparison to a Dutch age matched norm population	Lower vitality scores in HL survivors	More fatigue in 5-10 yr survivors than in norm population. Differences disappear after more than 10 yrs after treatment	Yes	12
Oldervoll (33) 2007 *	476	46 (21-73)	15.7-17 SD 89.5 and 82.6	RT, CT or CMT	Cross-sectional	81%	FQ	Yes, results partly compared to epresentative sample of Norwegian population	Prevalence of chronic fatigue HL survivors 30%, no comparison fatigue level to norm data	-	-	12
Rüffer (24) 2003	836	NR	5.2	RT, CT or CMT	Cross-sectional	61%	QLQ-C30 MFI	Yes, comparison to 935 age, gender and living area matched healthy controls	Higher fatigue in HL survivors, both QLQ C30 and MFI measured	Increasing fatigue with age, KPS, relapse, B-symptoms. No differences between: gender, treatment, stage	Small	12

Abbreviations: HL = Hodgkin lymphoma; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; POMS = Profile of Mood States; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; FQ = fatigue questionnaire; SF-36 = short-form 36; Facit-F = Functional Assessment of Chronic Illness Therapy-Fatigue; MFI = Multidimensional Fatigue Inventory; SeisQoL DW = Schedule for the Evaluation of Individual QoL-Direct Weighting.

* Studies reporting results from the same HL survivor cohort and norm population.

Table 5.3: Overview of studies on fatigue in HL survivors with comparison to normative data (continued)

Study	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm population	Fatigue outcome	Major findings	Clinically relevant difference	Quality Score
Bloom (9) 1993	85	32.2	3.1	RT or CMT	Cross-sectional	NR	POMS	Yes, comparison to testis carcinoma patients, gender matched	More fatigue and less return of energy in HL survivors compared with testis carcinoma patients	-	No	11
Joly (34) 1996	93	42 (23-85)	10 (4-17)	RT, CT or CMT	Cross-sectional	90%	EORTC QLQ-C30	Yes, comparison to 183 age, gender and city of residence matched healthy controls	Mean fatigue score significantly higher in HL survivors	-	Small	11
Ng (23) 2005	511	44 (16-82)	15 (5-32)	RT, CT or CMT	Cross-sectional	60%	FACIT-FSF-36	Yes, comparison to siblings of HL patients	Fatigue borderline significantly higher in HL survivors compared with siblings. Prevalence fatigue 37% HL survivors vs 27%.	Higher levels of fatigue in case of cardiac disease. No differences between gender, age, treatment or thyroid disease	No	11
Tulder (34) 1994	81	47 (25-77)	14 (10-18)	RT or CMT	Cross-sectional	92%	SF-36	Yes, comparison to hospital visitors, age and gender matched	Vitality HL survivors not significantly lower	-	Yes	11
Wettergren (32) 2003	121	47 SD 11.9	14 SD 64.9	RT, CT or CMT	Cross-sectional	62%	SeisQoL DW	Yes, results partly compared to random sample of 236 Swedish citizens	10% HL survivors mentioned fatigue, no comparison of fatigue to norm data	-	-	11
Brandt (37) 2010	98	NR (21-72)	3.5 and 11	HD-CT + SCT or CCT	Cross-sectional	64%	EORTC QLQ-C30	Yes, comparison to healthy German reference population	Fatigue significantly higher in both groups of HL survivors compared with norm	-	Medium	10
Gil (35) 2003	46	43 (15-80)	7.6 (0.8-22.1)	RT, CT or CMT	Cross-sectional	69%	EORTC QLQ-C30	Yes, comparison to 46 healthy individuals from medical faculty	Fatigue not significantly higher in HL survivors	No differences in fatigue between treatment	Small	10

Abbreviations: HL = Hodgkin lymphoma; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; HD-CT = high dose chemotherapy; CCT = conventional chemotherapy; POMS = Profile of Mood States; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; FQ = fatigue questionnaire; SF-36 = short-form 36; Facit-F = Functional Assessment of Chronic Illness Therapy-Fatigue; MFI = Multidimensional Fatigue Inventory; SeisQoL DW = Schedule for the Evaluation of Individual QoL-Direct Weighting.

Table 5.4: Association of patient, clinical and treatment characteristics with observed fatigue

Variable	No. of studies with positive relation / total no of studies investigating variable	No. of subjects with positive relation / total no of subjects in studies investigating variable	Type of relation
Age*	4 / 7	2332 / 3255	Increasing fatigue with older age
Sex*	2 / 7	977 / 3212	935 female more fatigue, 42 male more fatigue
Education*	1 / 2	459 / 970	More fatigue in lower educated
Systemic symptoms*	2 / 5	1771 / 2891	More fatigue if systemic symptoms present at diagnosis
Stage*	0 / 5	0 / 2200	No influence of stage on fatigue
Treatment*	2 / 11	380 / 3955	More fatigue after combined modality treatment
Time since diagnosis*	4 / 7	1479 / 2942	1311 decrease of fatigue over time, 168 increase of fatigue over time
Relapse*	1 / 4	836 / 1991	More fatigue after (treatment for) relapse
Smoking	1 / 2	511 / 1347	More fatigue in smokers
Psychiatry	2 / 2	932 / 932	More fatigue in patient with psychiatric comorbidity
Late complications	3 / 3	771 / 771	More fatigue in presence of late complications/comorbidity

* exclusion of overlapping results from studies reporting on the same HL cohort

39) did not report precise levels of fatigue, but reported on the course of fatigue over time, both showing decreasing fatigue over time after completion of treatment. Ganz *et al.* (8) showed a decrease of fatigue from 6 months after diagnosis, with fatigue levels returning to baseline level at two years after diagnosis.

Socio-demographic, clinical and treatment characteristics associated with fatigue

Among the 22 studies, 17 studied fatigue in relation to socio-demographic, clinical, or treatment-related characteristics. An overview of these characteristics and their association with fatigue is presented in Table 5.4. Overlapping results from studies reporting from the same HL cohort were excluded. Variables that were most frequently associated with fatigue were gender, age, stage of HL, treatment, time since diagnosis and occurrence of relapse (8, 9, 22-27, 29-31, 35, 38-41).

Seven studies examined the association of gender and levels of fatigue. Five studies found no relationship (8, 22-24, 40), while one large longitudinal study showed that women had statistically significant worse scores of fatigue as measured by EORTC QLQ-C30 and general fatigue as measured by the MFI, but failed to show a

relation between gender and the other fatigue dimensions of the MFI (39). In contrast, in a study of 42 HL survivors Norum *et al.* found that men had worse outcomes in fatigue scores than women (41).

Four out of seven studies found significantly higher fatigue levels in older patients (9, 22, 24, 39), while three other studies did not confirm this (8, 23, 40). None of the five studies relating initial stage of HL to levels of fatigue found a significant association (8, 22, 24, 26, 29, 40).

Eleven studies have investigated fatigue levels with different treatment strategies, such as radiotherapy versus chemotherapy or combined modality treatment. Nine of these studies, all cross-sectional in design, did not find any relationship (9, 22-24, 29, 35, 39-41). One longitudinal study did report higher fatigue levels with combined modality treatment 6 months after diagnosis when compared with radiotherapy alone, but differences between treatment arms disappeared over a longer time period and were most likely related to differences in duration between the two treatment arms (8). One cross-sectional study found higher fatigue scores after combined modality treatment when compared with chemotherapy or radiotherapy alone (38).

Time since diagnosis was examined in 7 studies. In four studies, time since diagnosis was associated with fatigue; one cross-sectional study showed higher fatigue prevalence rates over time (40) while 2 longitudinal studies and 1 cross-sectional study showed decrease of fatigue over time (8, 31, 39). Three studies did not find any relation between time since diagnosis and fatigue (22, 23, 29).

Three out of four studies did not find an association between occurrence of relapse and fatigue (22, 23, 40). One found higher levels of fatigue after relapse of disease (24). Other parameters, such as level of education or smoking were less frequently investigated and mostly showed conflicting results.

Conflicting data concerning variables associated with fatigue could not be explained by differences in length of follow-up duration or instruments used.

Late treatment sequelae or comorbidities and fatigue

Three cross-sectional studies focused specifically on the impact of late-treatment sequelae or comorbid conditions on levels of fatigue (23, 27, 40). Ng *et al.* compared 511 HL survivors with 224 siblings (23). They observed a modest difference in mean fatigue scores measured by the FACIT-F, and in multivariate analysis found a significant positive correlation of cardiac disease with fatigue. They did not find an association between adequately suppleted hypothyroidism and fatigue. In their 2013 follow-up study among the HL survivors, they showed a statistically significant worsening of fatigue over time, in those patients suffering from late cardiac or pulmonary

complications (28). Knobel *et al.* (27) found higher levels of fatigue in 92 HL survivors suffering of pulmonary dysfunction, and confirmed absence of higher levels of fatigue in survivors with treated hypothyroidism. However, they did not find an association between fatigue and cardiac disease.

Miltenyi *et al.* (40) found higher fatigue levels in HL survivors with late treatment complications in general.

Discussion

This systematic review, including 22 large studies that investigated prevalence of fatigue or fatigue levels in HL survivors, showed prevalence rates of 11-76% in HL survivors, compared with 10% in the general population. We also found 5-13% higher levels of fatigue in HL survivors when compared with the general population; differences that were mostly clinically relevant. There was some evidence that older age at diagnosis might lead to higher fatigue levels. Treatment modality and stage of initial HL did not seem to be associated with fatigue levels. Evidence for the influence of characteristics such as level of education, time since diagnosis, or relapse of disease was often contradictory.

Although HL is a relatively rare disease, its occurrence at a young age and the increasing numbers of long-term survivors reporting long-lasting fatigue and reduced vitality have prompted specific studies of fatigue among HL survivors. For 19 of the 22 included studies, (8, 9, 22-34, 36, 38, 39, 41) quality assessment scores ranged from 11 to 14, indicating a high methodological quality. Shortcomings were mostly lack of description of missing data (N=12) and lack of description of non-responders (N=6). The latter makes it more difficult to estimate potential selection bias. Another frequent shortcoming was lack of a prospective design (N=20).

The majority of the studies were cross-sectional by design, which makes them suitable for evaluating prevalence rates of fatigue, but limits the possibility to evaluate causal relationships between prognostic factors and fatigue. Reported associations were often contradictory, with the exception of the consistent finding that initial stage of HL did not impact fatigue rates.

Only two studies had a prospective, longitudinal design. Both studies showed a decrease in levels of fatigue over time. Ganz *et al.* (8) showed that fatigue levels in both treatment arms, measured by the SF-36, returned to baseline levels measured before start of treatment. These baseline levels, however, were lower than population fatigue levels measured by SF-36 in other cross-sectional studies (30, 31, 36), both in

HL survivors and in norm populations. This could be due to a patient selection bias, since the study accompanied a randomized trial on efficacy of different treatment strategies.

Concerning influence of treatment modalities on reported fatigue in these longitudinal studies, one study did not find different levels of fatigue between the two different treatment arms, while the other did. This may be due to the fact that fatigue was measured at a fixed time point of 6 months after diagnosis, without accounting for the difference in treatment duration between the radiotherapy alone group and the combined modality group. Twelve of the 13 cross-sectional studies addressing treatment modalities found no association with levels of fatigue. Although treatment modality may not have a direct impact on the risk of chronic fatigue, late treatment sequelae may. Research on associations between fatigue and comorbidities or late treatment complications is limited. A relation was suggested in three cross-sectional studies. However, only one of these studies compared the results for HL survivors with comorbidities to matched case controls. Levels of fatigue may also be negatively influenced by the presence of depression, since presenting symptoms may overlap between these conditions. There was only one study that combined measurement of fatigue and depression in a group of 457 HL survivors and found significant overlap (26).

When we limit the evaluation of prognostic factors to the studies with the highest quality scores (8, 22, 24, 25, 27, 29, 31, 39), influence of patient and treatment characteristics on levels of fatigue seems to be limited to increasing age.

Definition of fatigue is difficult and often subjective. Therefore, measurement of fatigue varies greatly between studies. It is often addressed through a variety questionnaires. It is unclear how these questionnaires correlate and if they would identify the same fatigue cases. Also, the interpretation of differences in fatigue scores between patients and norm populations remains difficult. Statistically significant differences do not necessarily imply clinical relevance. It was possible to determine clinical relevance of reported differences in fatigue levels between HL and population controls for 11 studies, of which 7 confirmed a clinically relevant higher fatigue score in HL survivors. These findings are in line with clinical practice, where a majority of the HL survivors report to suffer from the effects of chronic fatigue in their daily lives, while lack of clear predisposing factors limit treatment options. Optimal treatment of comorbidities and especially of anxiety and depression might be of benefit.

In conclusion, HL survivors are at serious risk for developing chronic fatigue and loss of vitality, since all except the two smallest studies showed 15-20% higher prevalence rates of fatigue compared with population controls. Most studies showed clinically relevant differences. Solid evidence for the influence of prognostic factors on fatigue is limited; gender, initial stage of disease and treatment modality do not

seem to play an important role in the development of chronic fatigue. To be able to provide a clinically meaningful treatment option for the chronic fatigue in HL survivors, focus should switch to the role of comorbidities, late treatment sequelae and the influence of psychological distress on developing fatigue in long-term HL survivors, preferably by assessing longitudinal data on HL survivors compared with a matched norm population.

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