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Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG)

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Abstract

Although treatment regimens for Hodgkin's lymphoma have become more sophisticated, little is known about the prevalence of fatigue in long-term survivors. Therefore, we investigated the fatigue status of long-term survivors of Hodgkin's lymphoma and a control group using a pre-validated questionnaire. In 1995/1996, we contacted 1981 patients, who were enrolled in the German Hodgkin Studies HD 1-6. All patients were treated according to the treatment protocols HD1-3 (1981–1988) and HD 4-6 (1988–1993). The patients with a current status of complete remission were asked to complete a quality-of-life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ C-30)) and a fatigue questionnaire (Multidimensional Fatigue Inventory (MFI)). The results were compared with the data from 935 controls, matched for age, gender and living area. Eight-hundred and eighteen questionnaires from the patients were available for analysis. The median time between the end of treatment and completing the questionnaire is 5.2 years. Fatigue levels of patients with Hodgkin's lymphoma are high, even years after treatment. Fatigue dimensions are significantly influenced by several clinical and non-clinical factors. Fatigue levels of Hodgkin's lymphoma patients are significantly higher than those of the control group. Further investigations are warranted to explore the effectiveness of treatment strategies for fatigue.

Keywords: Fatigue; Hodgkin's lymphoma; Long-term sequelae; Quality of life

1. Introduction

It has been demonstrated that quality of life (QoL) is an important outcome measure in oncology [1–3]. A review of the most important randomised clinical trials in Hodgkin's lymphoma (HD) at this time reveals that QoL is disregarded as a primary or even as secondary outcome measure. For the most part, retrospective analyses of long-term survivors of HD have been performed. These analyses have identified a substantial subgroup of patients who still carry a great burden resulting from the disease and its treatment even years after the end of active therapy [4–11]. A number of factors have been put forward contributing to a high risk of maladaptation, even years after cure, e.g. low income, unemployment and a low education level. In one investigation, 22% of the 273 patients studied met the criteria suggested for a psychiatric diagnosis [12]. Recently, fatigue, one aspect in the multidimensional concept of QoL, has become an issue of great interest. Fatigue comprises a wide range of impairments interfering with daily life and leading to a considerable loss in QoL. Fatigue is nowadays considered as a treatment or tumour side-effect as it is experienced by nearly all cancer patients. Still, it remains unclear what the main contributors are to this subjective factor. A Norwegian study showed that patients surviving HD were significantly more fatigued than the general population. In this analysis, disease stage was identified as a significant predictor of fatigue. Treatment characteristics showed no significant correlations [13].

We started this survey in order to investigate the prevalence of fatigue and to identify possible predictors within HD patients treated in the German Hodgkin Study Group (GHSG) trials.

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2. Patients and methods

The GHSG was founded in the late 1970s. In 1981, the first study was initiated, HD1-3. The second study, HD4-6, was started in 1988 and closed in 1993. Today, 321 centres are members of the GHSG and recruit patients, mainly in Germany, but also in Switzerland and Austria.

In 1995, the panel of the GHSG decided to introduce a QoL assessment into its studies. It was proposed to start with a cross-sectional study on all surviving and cured patients who were treated in the HD1-6 trials (1981–1993). Along with the investigation of the patients, a normal control population—matched to the patient group according to age, gender, and living area—was studied in order to generate reference data for comparisons (Table 1).

2.1. Quality-of-Life Questionnaire for Survivors (QLQ-S)

The European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ C30) was chosen as the standard questionnaire for assessing the main basic dimensions of QoL [14,15]. The QLQ C30 was developed according to the basic theoretical concept that QoL is a multidimensional construct rather than a uniform dimension of human life. Under the circumstances of a life-threatening illness, it is supposed that some dimensions of the perceived QoL are of greater importance to the individual than others and that these centrally important areas of QoL can be identified and should be primarily used for assessing the QoL of patients. It is further assumed that in illnesses such as oncological diseases, important dimensions exist among the different oncological diagnoses. Thus, the QoL questionnaire by the EORTC Quality of Life Study Group was designed to incorporate the main areas of QoL relevant for patients with cancer. The option of adding further parts of treatment and disease-specific modules was left open for adaptation to the aim and the endpoints of the respective trials. The questionnaire in its current version has known psychometric properties, was validated in two international cross-cultural multilingual field trials and is used in numerous trials in various language versions. Apart from the scale nausea/vomiting and four items addressing gastrointestinal side-effects and sleep disturbance, the entire QLQ C30 was used. Additional scales came from a German Testicular Cancer Trial Group addressing sexuality, partnership, strain from treatment and disease, and global retrospective evaluation of treatment. The Multidimensional Fatigue Inventory (MFI) was chosen to investigate five different areas of fatigue [16,17]. Similar to other questionnaires, the basic idea of the MFI is an multidimensional concept contributing to the symptom fatigue. The MFI distinguishes 5 areas of fatigue; general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. In this self administered questionnaire, every area is investigated by 4 questions. For all three parts, extensive validation from various studies was available regarding the psychometric properties. The basic concept followed the construct of the QLQ C30 with functional scales, symptom scales and single items. The response format used the known four or seven-point scales, the MFI used a five-point scale. After obtaining the permission of the respective copyright holders, the three different parts were incorporated in a combined questionnaire leaving each part unchanged in format and content. The combined questionnaire contained 62 questions in total, with 45 questions contributing to 14 scales, 14 single items, and three open questions. Because it was targeted at cured surviving patients, the questionnaire was called the "*QLQ-S*" (*Quality-of-Life questionnaire* for *S*urvivors). The questionnaire was designed as a self-administered patient questionnaire and currently is available in ten different language versions (Dutch, English,

Table 1
Study populations (GHSG patients and matched controls)

Hodgkin's survivors		Control persons from population registries (matched for age, gender, and size of living area to the Hodgkin's survivors)
Patients included in HD1-6: 1981–1993 $N = 2493$ in 129 centres	Patients identified for QoL study: 1995–1996 $N = 1369$ in 72 centres $N = 836$ (61%) Questionnaires returned	$N = 935$
Instruments		
Patient Identification Items		Normal Control Person Information
Patient Information		LSQ-N (45 life situation domains) self-report (normal controls)
LSQ-S (45 life situation domains) self-report (patients) time needed: approximately 20–30 min		time needed: approximately 20–30 min
OLQ-S (62 items) self-report (patients) time needed: approximately 10–20 min		OLQ-N (53 items) self-report (normal controls) time needed: approximately 10–20 min

GHSG, German Hodgkin Study Group; QoL, quality of life.

French, German, Italian, Polish, Portuguese, Slovenian, Spanish, Russian) that were developed according to the general and translation guidelines of the EORTC Quality of Life Study Group for QoL questionnaires for use within clinical trials [18]. The structure of the questionnaire is shown in Table 2.

The QLQ-S was modified for use within cross-sectional studies with normal controls and the items directly related to disease and treatment were omitted. The QLQ-N includes 53 items and contains the core parts of the QLQ-S.

2.2. The Life Situation Questionnaire (LSQ)

The LSQ addresses an extensive variety of life domains of surviving Hodgkin's patients comprising several areas of interest such as upbringing, education, history of professional life and current work status during treatment and at the time of investigation, marital and family situation, living circumstances, relationships to friends and others, social life and leisure activities, medical history including current status. In close collaboration with its French primary authors, the questionnaire was translated into German and adapted to form the Life Situation Questionnaire in the current versions. The main life situation domains (with 45 subdomains in total) are shown in Table 3 [19].

The questionnaire was developed into a patient version (*LSQ-S: Life Situation Questionnaire Survivors*) and a version for normal control persons (*LSQ-N: Life Situation Questionnaire Normals*).

To date, the original French and German versions are available. An English master version for further translations into other languages is under development.

Table 2
Structure of the Quality of Life Questionnaire for survivors[a]

Functional scales			Single items
I	Physical function	(5 items)	1. Dyspnoea
II	Role function	(2 items)	2. Dry mouth
III	Emotional function	(4 items)	3. Polyneuropathy
IV	Cognitive function	(2 items)	4. Infections
V	Social function	(2 items)	5. Financial difficulties
VI	Sexual function	(3 items)	6. Fear of childlessness
VII	Global QoL	(2 items)	7. Self-confidence affected[b,c]
			8. Emotional burden[b,c]
Symptom scales			9. Sex life affected[b,c]
I	Fatigue (EORTC)	(3 items)	10. Difficulties[b,c]
II	Pain	(2 items)	11. Overall emotional condition
			12. Partner relationship changed[b]
Fatigue scales (MFI)			13. Recommendation to others[b]
I	General fatigue	(4 items)	14. Agree to treatment again[b]
II	Physical fatigue	(4 items)	
III	Cognitive fatigue	(4 items)	Open questions
IV	Red. motivation	(4 items)	1. Decision different today
V	Red. activity	(4 items)	2. Most difficult consequence
			3. Other issues

7 Functional *(20 items)* and 2 Symptom *(5 items)* and 5 Fatigue *(20 items)* scales
Total: 59 Items and 3 Open questions

[a] Patient version.
[b] Disease-related items are omitted in the normal control version "QLQ-N" (53 items).
[c] by/of disease and treatment.

2.3. Analyses plan for QLQ-S

Different analyses were carried out in order to empirically confirm the scale structure of the QLQ-S for the given group of patients, to prove scale reliability and different aspects of validity. The way of analyses systematically used the approach of the EORTC Quality of Life Study Group for reliability and validity assessment of the QLQ-C30. Multi-trait scaling analysis was used to determine whether the items of the QLQ-S could be combined into a smaller number of scales. Item scale correlations were investigated and a Pearson coefficient of <0.40 was regarded as sufficient for item scale convergent validity. In addition, the correlations of each item with its own scale and with the other scales were analysed. A higher item scale correlation with its own scale than with the other scales was defined as a scaling success. The reliability of the multi-item scales was tested by use of the Cronbach's alpha coefficient. The internal consistency of a scale is regarded as sufficient, at least for group comparisons, if the Cronbach's alpha coefficient is >0.7. In order to obtain information about the clinical validity of the QLQ-S, two approaches were taken. First, correlations between the multi-item scales were analysed. Higher correlations were expected for scales with similar content, e.g. the different fatigue scales. Then, clinical parameters like gender, age ($\leqslant 40$ vs >40 years), clinical stage (CS I vs II vs III vs IV), systemic symptoms, Karnofsky performance score (KPS) at the time of diagnosis (100 vs <100),

Table 3
Domains of the Life Situation Questionnaire for Survivors (*LSQ-S*[a])

Hodgkin's lymphoma-related questions	Family/upbringing
Health problems due to HD and affecting daily life	Professional status (history)
Change of/in leisure activities, relationship to friends, education, partnership, sexuality	Financial situation
General health-related questions	Retrospective evaluation of treatment
Supportive measures	

HD, Hodgkin's disease.
[a] The *LSQ-N* is adapted from the *QLQ-S* for use with normal controls.

treatment group (early vs intermediate vs advanced), relapse (yes vs no), haemoglobin at time of diagnosis, haemoglobin at time of survey, tumour disease in family (yes vs no), number of tumours in family (0 vs 1 vs 2 vs 3), severe illnesses or accident (0 vs 1 vs 2 or 3 vs 4 or 5 vs 6 or more), smoker (yes vs no), number of cigarettes (1–5 vs 6–10 vs 11–20 vs >20) were used to constitute groupings for known group comparisons. Statistical differences between these patient subgroups were tested for by use of the one-way analysis of variance (ANOVA).

Beside the more psychometric analyses, further approaches included a probationary grouping of the patients with regard to their reported fatigue levels. As reference values, we used available data from normal control cohorts and from different patient groups during hospital in-patient treatments [6,12,18]. With fatigue levels of <20 on the fatigue scale of the EORTC QLQ C-30, no particular strain was assumed (probationary "normal level"), fatigue values of >40 were regarded as being connected with a potentially high strain (probationary "pathological level").

3. Results

3.1. Patient characteristics

Our study aimed to include all surviving patients in complete remission who were treated in the HD1-6 trials. The participating centres were asked to co-operate in tracing the treated patients and contacting them by mail. Seventy-two centres agreed to participate. Patients received the questionnaires, QLQ-S and LSQ-S, by mail via the local hospitals and returned their questionnaires directly to the study centre in an encoded way.

The 72 participating centres recruited 1688 patients from HD1-6 (total GHSG: 2493 patients). With the help of local physicians, the questionnaires were mailed to 1369 patients. For the remaining 319 patients, no current address was available from the local physicians. The mailing process was rather complicated since three different methods had to be used. For the German centres, either the prepared envelopes with the patient's address already affixed were sent to the local centres and distributed from there, or the centres received blank envelopes with the questionnaires and did the mailing themselves. For the Swiss centres, the mailing had to be done through the central trial office of the Swiss cancer research group (SIAK). Assuming that all addressed patients really received their questionnaires, the response rate was 61% (836 forms) which is in accordance with the rates reported in the literature [20]. The completeness of forms was very high. Only 13 questionnaires had to be excluded because of missing data, and 5 had to be excluded for missing clinical data-sets. The age distribution of the responding patients was comparable to the total study population. The median time from diagnosis to completing the questionnaire was 5.2 years. The median age of the patients at the time of diagnosis was 31 years (range 15–72 years) (Table 4).

There were 390 women (48%) and 428 men (52%) with the following histologies at the time of the HD diagnosis: lymphocyte-predominant 81 (10%), nodular sclerosis 469 (57%), mixed cellularity 212 (26%), lymphocyte depleted 21 (23%), and non-classified 35 patients (4%). There were 113 patients (14%) with

Table 4
Patient's characteristics I

	Patients $n=818$ (%)
Age median (range)	31 (15–72) years
Age	
≤40 years	589 (72)
>40 years	229 (28)
Relapse	
Yes	94 (11)
No	724 (89)
Haemoglobin at time of diagnosis	
<120 g/l	223 (27)
120–140 g/l	338 (41)
>140 g/l	246 (30)
missing data	11 (1)
Haemoglobin at time of survey	
<120 g/l12	28 (3)
−140 g/l	179 (22)
>140 g/l	206 (25)
missing data	405 (50)
Tumour disease in family	
yes	353 (43)
no	463 (57)
missing data	2 (<1)
Number of tumours in family	
0	359 (44)
1	240 (29)
2	131 (16)
3	88 (11)
Severe illnesses or accidents	
0	325 (40)
1	186 (23)
2 or 3	174 (21)
4 or 5	78 (10)
6 or more	55 (7)
Smoker	
no	609 (74)
yes	205 (25)
missing data	4 (<1)
Number of cigarettes	
1–5	24 (12)
6–10	49 (24)
11–20	94 (46)
>20	37 (18)
missing data	1 (<1)

PS/CS I; 348 patients (43%) with PS/CS II, 240 patients (29%) with PS/CS III and 117 patients (14%) with PS/CS IV. Treatment for HD consisted of radiotherapy alone in 112 patients (16%), combined modality treatment in 353 patients (51%), and mainly chemotherapy in 224 patients (33%). No detailed treatment-related information was available for 129 patients. 94 patients (11%) experienced a relapse of their HD (Tables 4 and 5).

A comparison of characteristics of patients in the cross-sectional study and the total number of the HD1-6 study patients showed no differences. Beside gender (3.6% more women and 3.6% less men in the QoL assessment group compared with the total sample), there were no differences regarding the clinical characteristics between responding patients and those who did not return the questionnaires (Table 5).

3.1.1. Quality-of-Life questionnaire for the Survivors (QLQ-S)

The psychometric evaluation of the QLQ-S resulted in most cases in item scale correlations which were above the 0.40 criterion for sufficient item convergent validity (exceptions were physical functioning and role functioning). The lowest value occurred for one item from the fatigue scale Reduced Activity ($r=0.62$), the mean value for all 14 scales was $r=0.85$. Item discriminant validity could be demonstrated by a scaling success of all items regarding their respective scales. The reliability could be confirmed by very satisfactory Cronbach's alpha coefficients (0.71–0.95), only the fatigue scale Reduced Motivation scored 0.65, a little lower than the 0.7 criterion. As previously known and mentioned above, the scales physical and role functioning did not perform within the required range (Cronbach's alpha of physical: 0.56 and role functioning: 0.28), but this was due to the scale construction (yes/no answer format) and the skewed distribution (pronounced ceiling effects) within the investigated patients. Furthermore, we investigated the basic psychometric properties of the QLQ-S in different subgroups of patients and there were little or no differences for gender (male vs female), age (<40 years vs >40 years) and relapse (yes vs no). All scores were linearly transformed into a scale from 0 to 100, high levels representing a high functioning for the functioning scales or high symptom levels for the symptom and fatigue scales.

Table 5
Patient's characteristics II

	Patients with QoL $N=818$%	Without QoL *(non-responders)* in% ($N=523$)	Total group HD1-6 in% ($N=2502$)
Male	428 (52)	59	56
Female	390 (48)	41	44
Stage[a]			
PS/CS I	113 (14)	16	15
PS/CS II	348 (43)	44	44
PS/CS III	240 (29)	26	27
PS/CS IV	117 (14)	15	14
Treatment protocol according to stage	$N=689$ (%)	in% ($N=405$)	in% ($N=1948$)
Early	112 (16)	19	19
Intermediate	353 (51)	45	49
Advanced	224 (33)	37	34
B-Symptoms	$N=817$ (%)	in% ($N=521$)	in% (N=2493)
No	483 (59)	58	60
Yes	334 (41)	43	41
Histology[b]	$N=818$ (%)	in% ($N=523$)	in% ($N=2502$)
LP	81 (10)	11	10
NS	469 (57)	54	55
MC	212 (26)	28	28
LD	21 (3)	3	2
Unknown	35 (4)	5	4
Karnofsky-performance status	$N=787$ (%)	in% ($N=428$)	in% ($N=2385$)
90–100	467 (59)	55	57
80–90	290 (37)	38	37
<80	30 (37)	6	6

[a] PS: pathological stage, CS: clinical stage
[b] LP = lymphocytes predominant; NS = nodular sclerosis; MC = mixed cellularity; LD = lymphocytes-depleted.

3.1.2. Fatigue pattern in long-term survivors of HD

The mean score for the fatigue scale from the QLQ-C30 was 36.5 and for the General Fatigue, as part of the MFI was 37.6. The other dimensions of the MFI were as follows: Physical Fatigue 32.6, Reduced Activity 28.0, Reduced Motivation 19.8 and Mental Fatigue 26.6.

These results did not appear to be affected by the time between end of therapy and the survey. Patients with a follow-up of 3, 5 or 7 years showed similar results in the different dimensions of fatigue (data not shown).

3.1.3. Fatigue and patient, disease and treatment characteristics

In Table 6, the results of the univariate analysis for the groups with different patient, disease and treatment characteristics are shown.

The following characteristics showed statistically significant differences for all dimensions of fatigue: age ($P<0.01/0.001$), systemic symptoms ($P<0.01/0.001$), KPS ($P<0.01/0.001$), and the occurrence of a relapse ($P<0.05/0.001$). An experience of accidents or severe illnesses was significant for fatigue, general fatigue, physical fatigue, reduced activity ($P<0.001$), the number of cigarettes smoked per day was significant for fatigue, reduced activity, reduced motivation ($P<0.05/0.01$), gender was significant for general fatigue ($P<0.05$), haemoglobin at the time of diagnosis, tumour disease in the family, and the number of tumour diagnoses in the family were significant for MF ($P<0.05$). Clinical stage, treatment group, and haemoglobin at the time of the survey revealed no significant differences in any of the fatigue dimensions.

Table 6
Fatigue dimensions (QLQ C-30 and MFI) and patients' characteristics

	Fatigue QLQ-C30 *P* value	General Fatigue MFI *P* value	Physical Fatigue MFI *P* value	Reduced Activity MFI *P* value	Reduced Motivation MFI *P* value	Mental Fatigue MFI *P* value
Gender	NS[a]	*	NS	NS	NS	NS
Age (years)	***	***	***	***	***	**
Clinical stage	NS	NS	NS	NS	NS	NS
Systemic symptoms	**	**	**	***	***	***
Karnofsky index (KPS)	**	***	***	***	***	***
Treatment group	NS	NS	NS	NS	NS	NS
Relapse	*	*	***	***	*	*
Haemoglobin at the time of diagnosis	NS	NS	NS	NS	NS	*
Haemoglobin at the time of survey	NS	NS	NS	NS	NS	NS
Tumour disease within family	NS	NS	NS	NS	NS	*
Number of tumours within family	NS	NS	NS	NS	NS	*
Severe illnesses or accidents	***	***	***	***	NS	NS
Smoker	NS	NS	NS	NS	NS	NS
Number of cigarettes	**	NS	NS	*	*	NS

QLQ30, Quality of Life Core 30. MFI, Multidimensional Fatigue Inventory. $P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.
[a] NS = non significant.

3.1.4. Fatigue in HD compared with a matched control group

Along with the investigation of the patients, a normal control population—matched to the patient group for age, gender and the size of living area (population)—was studied in order to generate reference data for comparisons. 935 responded and they were from the normal control population of the area of greater Cologne. The controls were asked to fill in the same questionnaires as the patients (N version: which is the modified version for controls where questions regarding HD and changes since first diagnosis of HD were adapted to be suitable for normal persons). Table 7 summarises the comparison of several different characteristics between the normal controls and the patient group indicating the effect of disease and treatment on variables, such as professional life and sexual activities.

Levels of fatigue were, in general, significantly higher in the patient group compared with the controls. This was true for all dimensions of the MFI and the QLQ-C30 (Table 8).

Table 7
Significant differences between the patient group and normal controls

	HD-patients	Normal controls	
Median age at time of survey (years)	37.1	35.5	
	%	%	*P* value
Male gender	52	46	0.005
Higher education parents	15	8	0.001
Higher profession father	23	29	0.007
Higher education	26	38	0.001
Living as a couple	66	76	0.001
No children	46	41	0.03
Profession today			0.001
w/o work	5	4	
unable to work	15	2	
retired	<1	5	
Smoking	33	25	0.001
Number of daily cigarettes			0.05
1–5	12	14	
6–10	24	16	
11–20	46	45	
>20	18	26	
Alcohol consumption			0.001
Increased	2	7	
Decreased	18	12	
No change	80	81	
Tumour disease in family	57	47	0.001
Drug intake	57	44	0.001
Sexual activities			
More	6	19	0.001
Less	31	34	
No change	63	47	
Change of sexual activities because of disease	47	8	0.001

w/o, Without.

3.2. Discussion

Our results suggest that: (1) fatigue levels of patients with HD are high, even years after treatment. (2) Fatigue dimensions are significantly influenced by several clinical and non-clinical factors. (3) Fatigue levels of HD patients are significantly higher than those of a matched control group.

As shown in previous studies, the fatigue levels of our study sample of long-term survivors of HD were high [19,21,22]. With a median follow-up of 5.2 years, patients showed elevated fatigue patterns without any

Table 8
Fatigue levels of patients controls

	Hodgkin's patients ($N=818$) mean (± standard deviation)	Controls ($N=935$) mean (± standard deviation)	P values
Fatigue scales			
Fatigue (QLQ C30)	36.5 (±29.0)	30.0 (±24.7)	<0.001
General fatigue (GF)	37.6 (±29.1)	30.9 (±23.2)	<0.001
Physical fatigue (PF)	32.6 (±29.2)	25.0 (±24.2)	<0.001
Reduced activity (RA)	28.0 (±26.1)	21.4 (±21.8)	<0.001
Reduced motivation (RM)	19.8 (±20.1)	16.9 (±18.1)	<0.001
Mental fatigue (MF)	26.6 (±26.8)	21.8 (±23.5)	<0.001

disease activity. These levels were not affected by the time between the end of therapy and the survey.

Several clinical and non-clinical factors were investigated in relation to the occurrence of fatigue. The following characteristics were shown to be significant for all dimensions of fatigue: age, systemic symptoms, KPS and the occurrence of relapse. In a Norwegian study, only age and clinical stage I/IIB could be identified as predictors for higher fatigue levels [13]. Furthermore, some non-clinical characteristics also had a strong correlation to certain dimensions of fatigue. However, in contrast to acute treatment-related fatigue, haemoglobin levels had hardly any influence on fatigue in our sample of long-term survivors of HD. The correlation between clinical features at the time of first diagnosis and the expressed level of fatigue did not seem to be very strong. Nevertheless, significantly different fatigue levels were found between long-term survivors of HD and those surviving testicular cancer [23].

Compared with normal controls, long-term survivors of HD showed significantly higher fatigue levels. Although both groups were matched for age, gender and living area (population) several differences could be identified. First, the response rate (in sending back the questionnaires) was different; 61% for the patient cohort and 29% for the control group. The two groups also showed significant differences in several other characteristics (Table 7). Whether these differences influenced the fatigue levels observed or whether these differences are influenced by fatigue itself, e.g. sexual activity, remains to be investigated in more detail.

Our investigation shows the importance of including questions on a patients lifestyle that may help to explain the increased patterns of fatigue.

In order to further enhance the effectiveness of treatments and to lower the acute and late side-effects as much as possible, more information is needed about how patients cope with illness and the late effects of treatment after returning to a normal life.

In summary, survivors expressed a high level of fatigue. Thus, increased fatigue is a common late effect in patients, even when there is no sign of recurrent disease. Assuming that fatigue has a strong impact on QoL, the diagnosis and treatment of fatigue is therefore important. The efficacy of different therapeutic strategies still has to be demonstrated although cognitive behavioural therapy and aerobic exercises have already shown promising results [24,25].

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