Background: Fatigue is a frequent and severe problem after treatment of patients with hematological malignancies. This symptom has been associated with anemia, reduced physical performance, mood, endocrine disorders and impaired nutritional status. Recently, it has been suggested that fatigue can be related to a persistent activation of the immune system with increased production of proinflammatory cytokines. However, there is no conclusive evidence regarding the role of the immune system in the origin of fatigue in cancer patients.

Patients and methods: We evaluated the correlation of fatigue with thyroid function, markers of immune activity [interleukin (IL)-1α, IL-1 soluble receptor, IL-6, C-reactive protein and neopterin], liver and kidney function, mood and physical ability in 71 patients with hematological malignancies. All patients had been free of relapse and not received treatment (chemotherapy, radiotherapy or immune modulators) for at least 3 months.

Results: Fatigue was related to depression ($r = 0.84; P < 0.0001$) and reduced performance status ($r = -0.61; P < 0.0001$). However, there was no correlation between fatigue and thyroid, liver and kidney function, anemia, albumin concentration or markers of immune activity (all $r$-values $< 0.20; P > 0.05$).

Conclusions: We conclude that fatigue in relapse-free patients with hematological malignancies is associated with depressive mood and reduced physical performance, but not with impairment of thyroid function, anemia or persistent activation of the immune system.

Key words: correlation analysis, fatigue, hematological malignancies

Introduction

Cancer-related fatigue is defined as an unusual and persistent sense of tiredness that can occur during or after treatment, may affect both physical and mental ability, and is not relieved by rest [1]. This symptom is the most common and distressing problem of cancer patients after treatment [2, 3]. For many patients, fatigue is severe and imposes limitations on normal daily activities. Several factors (anemia, impaired nutritional status, sleep disturbances, changes in the concentration of cytokines due to the interaction between tumor and host immune system, mental and social status, and reduced level of activity) have been proposed to be related to fatigue in this setting [1, 4]. However, the origin of this symptom is not yet fully understood.

Psychological factors play an important role in the origin of fatigue [4]. However, the relationship between depression and cancer-related fatigue is not clear. While cohort studies have frequently detected an association between the two disorders [5–7], a recent randomized controlled trial has shown that antidepressants may improve mood but not reduce fatigue in cancer patients [8].

One possible cause of fatigue in cancer patients is a treatment-related disturbance of the endocrine system. Chemotherapy may result in an impaired function of Leydig cells and therefore in reduced production of sexual hormones. In fact, lower testosterone concentrations and increased luteinizing hormone and follicle-stimulating hormone levels have been reported in patients after chemotherapy [9]. However, the severity of fatigue did not differ between cancer patients with Leydig cell dysfunction and those with normal testosterone concentrations [10]. Impaired thyroid function has also been suggested to cause cancer-related fatigue [11]. Hypothyroidism has been observed in patients undergoing radiotherapy for the treatment of hematological malignancies or solid
tumors of the head, neck and breast [12, 13]. Furthermore, thyroid function may be affected by conditioning with total body irradiation for bone marrow transplantation, therapies with biological mediators like interferon or interleukin 2 (IL-2), and several chemotherapy protocols [14, 15]. Low concentrations of thyroid hormones may result in tiredness and rapid fatigue. However, no study has evaluated the correlation between thyroid function and fatigue in cancer patients. Therefore, the association between the two phenomena remains speculative. In fact, cancer-related fatigue is much more frequent than treatment-related thyroid dysfunction [16].

Finally, several co-morbidities may generate fatigue, among them increased concentrations of nitrogen products due to renal or hepatic failure, impaired physical performance caused by chronic left ventricular failure, or malnourishment due to mucositis or after gastrointestinal resections. Anemia is a frequent problem during and shortly after cancer treatment. Low hemoglobin concentrations may be a relevant cause of fatigue in this setting. However, studies on the relationship between anemia and fatigue in cancer patients have yielded contradictory results [17, 18].

A significant correlation between fatigue and albumin concentration has recently been reported in patients with hematological malignancies undergoing chemotherapy [19]. However, the mechanisms linking fatigue and hypoalbuminemia have not yet been elucidated. Low albumin concentrations may be related to reduced nutrient intake or increased protein loss due to mucositis or renal failure, but may also reflect a defect in the hepatic synthesis of proteins as a result of the acute phase reaction. It has been suggested previously that fatigue in cancer patients may be related to persistent activation of the immune system and to increased production of proinflammatory cytokines [20]. In fact, fatigue is frequently caused by treatment with immunomodulators (interferon and interleukins), which induce proinflammatory cytokine synthesis. Furthermore, chronic fatigue syndrome patients may have increased serum IL-6 concentrations [21]. Increased activity of this cytokine has also been detected in lymphoma patients with a poor performance status [22].

A recent study evaluated the activity of proinflammatory cytokines in breast cancer patients who had been free of relapse for >1 year [23]. Concentrations of IL-1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor type II (sTNF-RII) and neopterin were higher in patients with increased fatigue scores than in those with lower ones. The authors suggest that persistent activation of the immune system may be involved in the development of long-lasting fatigue. However, in this study, the activity of all assessed cytokines remained within the normal range. Thus, the significance of the association between activation of the immune system and fatigue is not clear.

Based on these considerations, we evaluated the correlates of fatigue in patients with hematological malignancies who were free of relapse after treatment.

**Patients and methods**

All outpatients with hematological malignancies in remission who attended the Department of Hematology and Oncology of the Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, between August 2001 and February 2002 were considered for participation (n = 85). Inclusion criteria were age 20–75 years, histologically confirmed hematological malignancy and the ability to understand written German. Exclusion criteria were chemotherapy, radiotherapy or immune therapy in the 3 months preceding the study, immunosuppression, treatment with glucocorticoids or psychostimulants, associated psychiatric, muscular, cardiovascular or pulmonary disease, fever or signs of infection in the week preceding recruitment, or relapse. Fourteen patients who had one or more exclusion criteria were retired from the study and 71 patients were recruited for the trial (Table 1). The study was approved by the institutional ethics committee and all patients provided written informed consent.

Following physical examination, all patients completed two self-administered questionnaires, the fatigue module of the Functional Assessment of Cancer Therapy (FACT) questionnaire [24] and the Center of Epidemiological Studies Depression Scale (CES-D) [25]. The fatigue module of the FACT questionnaire consists of 13 questions and allows an evaluation of the severity of fatigue in the preceding week. The CES-D is a self-report scale for assessing depression and evaluates symptoms in the 7 days preceding the test. Higher CES-D scores and lower FACT scores indicate greater mood disturbance (i.e. more severe depression or fatigue). All patients needed <10 min to complete both questionnaires.

The performance status of patients was evaluated using a list of activities ranked from less intense to most strenuous according to their energy cost in metabolic equivalents (METs; 1 kcal/kg/h). Patients were asked about the activities they could carry out and a cut-off point was set at the last activity they could perform. Energy cost of activities in metabolic equivalents was obtained from standard tables [26]. Patients were included in one of four functional categories: physical performance ≤1 MET, 1–3 METs, between 3 and 6 METs, and >6 METs.

Blood samples were obtained after a 20-min rest between 9:00 a.m. and 11:30 a.m. Serum samples were separated according to standard procedures and stored at −20°C for subsequent batch testing. Complete blood count and hemoglobin concentration, thyroid function (TSH, T3 and T4), creatinine, urea, serum electrolytes, hepatic enzymes, bilirubin and albumin were assessed by standard laboratory procedures. C-reactive protein was assessed using a high-sensitivity enzyme-linked immunosorbent assay.

**Table 1. Baseline data of patients in the study**

<table>
<thead>
<tr>
<th>Age [mean ± SD (range)]</th>
<th>51 ± 13 (21–72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>41/30</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>23</td>
</tr>
<tr>
<td>Low-grade non-Hodgkin’s lymphoma</td>
<td>11</td>
</tr>
<tr>
<td>High-grade non-Hodgkin’s lymphoma</td>
<td>20</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>9</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic lymphatic leukemia</td>
<td>6</td>
</tr>
<tr>
<td>Time since first diagnosis (months) [mean ± SD (range)]</td>
<td>50 ± 51 (4–246)</td>
</tr>
<tr>
<td>Time since last therapy* (months) [mean ± SD (range)]</td>
<td>28 ± 27 (3–132)</td>
</tr>
</tbody>
</table>

*Chemo-, radio- or immunotherapy. SD, standard deviation.
Fatigue has been related to changes in several laboratory parameters. However, it is not known if there is a continuous relationship between the severity of this symptom and the deviation of laboratory values from the normal range. In certain disorders (i.e. liver or renal failure), laboratory parameters must reach a threshold before the patients develop symptoms; we therefore carried out two statistical work-ups. In the first work-up, we evaluated the association of fatigue with age, diagnosis, mood status, renal, hepatic and thyroid function, concentration of IL-1α, IL-1rs, IL-6, neopterin, C-reactive protein, albumin, hemoglobin and severity of anemia (calculated as the difference between the lower normal limit for gender and the actual hemoglobin concentration) with a stepwise multiple regression test. Since impairment of renal and hepatic function may be caused by inflammatory or autoimmune disorders, we also analyzed the correlation between immune activity and fatigue in patients with normal renal and hepatic function (n=44).

In the second statistical work-up, we identified patients in the lowest and highest quartiles of fatigue scores and compared the above-mentioned factors in both groups with the Mann–Whitney test. Finally, we compared the fatigue scores of patients with impaired renal, hepatic or thyroid function, or elevated interleukines, C-reactive protein or neopterin concentrations with the rest of the sample. All values are expressed as mean ± standard deviation, with ranges in parentheses. A value of r>0.30 was accepted to indicate relevant correlation. A power calculation showed that a sample of 67 patients was necessary to detect this correlation with a probability of an error of <5% (P value <0.05) and of a β error of <20%.

Results

Three patients had a known impaired thyroid function and received hormone substitution. Laboratory tests detected hypothyroidism in another patient, impaired renal function in eight patients, hepatic dysfunction (elevated gamma-aminotransferase, glutamate-oxalacetate transaminase, glutamate-pyruvate transaminase or bilirubin) in 23 patients, and anemia in 13 patients. All anemia patients had a hemoglobin concentration >11 g/dl (mean 12 ± 1.0 g/dl); according to institutional guidelines, none of them required treatment for anemia (blood transfusion or erythropoietin). C-reactive protein, IL-6, IL-1ra and neopterin concentrations above the normal range were detected in 11, 12, 13 and eight patients, respectively. Mean fatigue scores of these patients were not higher than those of patients with normal laboratory values (Figure 1). Severity of fatigue was related to depression (r = −0.84; P<0.0001) and impairment of performance status (r = 0.61; P<0.0001). These factors explained 73% of the variance of fatigue (β, −0.84; P<0.0001). Fatigue did not correlate with diagnosis, time since chemotherapy, renal, hepatic or thyroid function, severity of anemia, serum albumin concentration, activity of proinflammatory cytokines, neopterin or C-reactive protein [all r-values <0.20; all P-values non-significant (see Table 2)]. When only patients with normal renal and hepatic function were considered (n=44), fatigue was not related to the serum concentration of the mentioned cytokines (all r-values <0.10; P>0.05). Depression scores and performance status of patients with fatigue scores in the upper and lower quartile were significantly different [depression score 2.3±2.7 compared with 22.3±9.6, respectively (P<0.0001);
performance status 3.5 ± 0.5 compared with 2.1 ± 0.9, respectively (P < 0.0001). However, the statistical analysis showed no difference in the laboratory values of the two groups (all P values non-significant) (Figure 2).

Discussion

Impaired performance status seems to be a crucial component of cancer-related fatigue syndrome. In fact, the present and previous studies have observed a relevant correlation between fatigue and physical performance [7]. Furthermore, endurance and resistance training programs not only improve physical performance but also reduce fatigue in cancer patients [27–30]. However, fatigue is a multidimensional problem. While some of the complaints reported by cancer patients with fatigue (i.e. no capacity for physical exertion, loss of stamina) may be related to an impaired performance status, others (i.e. somnolence, forgetfulness, lack of motivation, difficulty to concentrate) are probably independent of physical capacity and may therefore have other causes.

One possible explanation for these symptoms is an altered endocrine function. Hypothyroidism has been observed after chemo- or radiotherapy [12–16], and may cause impairment of mental function, reduction of stamina and rapid fatigue. However, in the present study, we did not find an association between thyroid function and fatigue.

In patients with active disease, a reaction against neoplasia causes phenomena like impaired hematopoiesis, B-symptoms and fatigue. Persistent activation of the host’s immune system has been considered a possible cause of fatigue in cancer patients after treatment [20]. However, the results of the present study speak against this hypothesis. The lack of association between C-reactive protein concentration (the principal marker of the acute phase reaction), IL-6 (a sensitive early indicator of inflammation), IL-1 and IL-1ra (two critical indicators of immune activity), and neopterin (a marker of the stimulation of cell-mediated immune response) on the one hand, and fatigue on the other hand, suggests that, in patients free of relapse after treatment, this symptom is not related to persistent activation of the immune system.

The strengths of the present study are a homogeneous population, the simultaneous assessment of fatigue, depression and performance status with independent tools, and the evaluation of laboratory parameters. However, there are also some methodological limitations.

We evaluated the patients’ performance status using a list of regular activities ranked by their energy cost in metabolic equivalents. Several fatigue questionnaires use a variant of this method to assess the physical limitations of cancer patients. However, these instruments only allow a gross evaluation of performance status. Maximal oxygen uptake is the gold standard for determining physical performance [31], but it relates poorly to everyday physical activity, patient symptoms and quality of life [32]. In fact, we have previously reported a low correlation between maximal oxygen uptake and fatigue in cancer patients [7]. Furthermore, maximal oxygen uptake depends strongly on age and gender. Evaluating the performance status with scales is easier and less expensive than assessing maximal oxygen uptake and does not require laboratory equipment. However, information obtained from questionnaires may be biased by expectancy and subjective appreciation of physical limitations, and may not reflect the patients’ actual experience.

The cross-sectional design of the present study may be seen as a limitation. Fatigue is a chronic phenomenon and may vary in the course of the disease. Longitudinal studies can provide a better understanding of the causes of cancer-related fatigue. However, changes in laboratory values over time are most likely related to acute events (i.e. infection or concurrent disease). Since patients with co-morbidities or signs of infection in the week preceding assessment were not included in the study, we feel that our results reflect a genuine lack of association between fatigue and thyroid, as well as immune, hematological, renal and hepatic function.

In the present study we evaluated possible biological and immunological mechanisms of fatigue. However, this symptom is a multifactorial phenomenon and may be influenced by social, demographic and psychological factors. In fact, psychosocial interventions, which are unlikely to modify physical performance or endocrine function, may reduce fatigue in cancer patients [33–35]. Impaired physical performance and depression seem to be critical components of the cancer-related fatigue syndrome. However, the association between the two factors has not yet been clarified. Impaired physical performance can result in increased dependence, decreased self-esteem, reduced social activities, restricted family life and a pessimistic mood. Furthermore, a reduced performance
status can be interpreted by the patient as a sign of poor health and increase his or her psychological distress. On the other hand, depressed and anxious patients are more likely to limit outdoors activities and resort to a passive lifestyle; this can result in muscular deconditioning and in a loss of physical performance [7]. Hence, it is not clear whether mood disturbance is a consequence or cause of the impaired physical performance, or if both disturbances are related to a third factor.

Our findings also have therapeutic implications. In the recent past, several publications have underlined the role of anemia as a major cause of fatigue in cancer patients undergoing chemotherapy. However, the findings of the present and other studies [17, 18] show that chronic fatigue not may be related to hemoglobin concentration. In fact, in patients with neoplastic diseases, treatment with erythropoietin sometimes results in a substantial increase in hemoglobin concentration, but only a marginal reduction in fatigue scores [36–38].

We concluded that in the relapse-free patients with hematological malignancies studied, fatigue was not related to anemia, impairment of thyroid, liver or renal function, or persistent activation of the immune system. However, these phenomena may cause persistent fatigue after treatment in certain patients. Furthermore, fatigue is associated with depression and impaired performance status. Therefore, the diagnostic work-up of patients with cancer-related fatigue should include the evaluation of labor parameters, psychological status and physical performance.

References