İleri Evre Akciğer Kanseri Olgularında Yorgunluk ve Güçsüzlükle İlişkili Faktörler

Correlates of Fatigue and Weakness in Advanced Lung Cancer Patients

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ÖZET

Amaç: Akciğer kanserli hastalarda yorgunluk problemiyle gittikçe daha fazla karşılaşılmaktadır. Bu çalışmanın amacı küçük hücreli dışı akciğer kanseri (KHDAK) olgularında yorgunluk ve güçsüzlükle ilişkili faktörleri araştırmaktır.

Gereç ve Yöntem: Altmış üç ileri evre erkek KHDAK hastası ve yaş ile cinsiyet-uyumlu 25 kontrol çalışmaya dahil edildi. Katılımcıların yorgunluk skorları "3-item fatigue subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30" (EORTC QLQ-C30) ile değerlendirildi. Güçsüzlük ölçeği olarak "visual analogue scale" (VAS) kullanıldı.

Bulgular: Kanser olgularının yorgunluk ve güçsüzlük skorları kontrollerden belirgin derecede daha yüksekti. Pozitif akut faz reaktanları CRP, lökosit, ferritin, trombosit ve fibrinojen, KHDAK grubunda kontrollerden yüksekti. TSH (tiroid-uyarıcı hormon), fT3 (serbest triiodotironin) ve testosteron düzeyleri kanser grubunda kontrollerden daha düşüktü ama kortizol düzeyinde farklılık yoktu. Yorgunluk skoru güçsüzlük skoru, kanserin evresi, lökosit ve trombosit sayıları ile pozitif; vücut kitle indeksi, hemoglobin, fT3, albümin ve transferrin ile negatif korelasyon gösteriyordu. Güçsüzlük skoru kanserin evresi ile pozitif; fT3, albümin ve transferrin düzeyleri ile negatif korelasyon gösteriyordu. CRP ile hem yorgunluk, hem de güçsüzlük skorları arasında pozitif korelasyon saptandı. Yorgunluk ve güçsüzlük skorları ile yaş, sigara yükü, lenfosit, kolesterol, ferritin ve fibrinojen düzeyleri arasında korelasyon yoktu.

Sonuç: Yorgunluk ileri evre KHDAK olgularında önemli bir semptomdur ve sistemik inflamatuar yanıtla ilişkilidir. Akciğer kanseri olgularının yorgunluk ve güçsüzlük değerlendirmesini de içeren geniş kapsamlı bir bakıma ihtiyacı vardır.

Anahtar kelimeler: Yorgunluk, akciğer kanseri, sistemik inflamasyon, kas güçsüzlüğü

ABSTRACT

Aim: Fatigue is increasingly recognized as a troublesome problem in patients with lung cancer. The aim of this study was, therefore, to investigate the correlates of fatigue and weakness with non-small cell lung cancer (NSCLC) patients.

Materials and Methods: Sixty three male advanced-stage NSCLC patients and 25 age and sex-matched controls were included in the study. Fatigue scores were evaluated by "3-item fatigue subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30" (EORTC QLQ-C30). VAS (visual analogue scale) was used as a measure of weakness.

Results: Fatigue and weakness scores of the cancer patients were significantly higher than the controls. The positive acute phase reactants, i.e., CRP, leucocyte, ferritin, thrombocyte and fibrinogen were higher in NSCLC group than in the controls. TSH (thyroid-stimulating hormone), fT3 (free triiodothyronine) and testosterone levels were lower in the cancer group whereas there was no difference in cortisol levels of both groups. Fatigue score was positively correlated with weakness score, stage of the cancer, leucocyte and thrombocyte counts; and was negatively correlated with body mass index, hemoglobin, fT3, albumin and transferrin levels. Weakness score was positively correlated with stage of the cancer and negatively correlated with fT3, albumin and transferrin levels. CRP was positively correlated with both fatigue and weakness scores. Fatigue and weakness scores were not correlated with age, cigarette-burden, lymphocyte, cholesterol, ferritin and fibrinogen levels.

Conclusion: Fatigue is a prominent symptom in advanced NSCLC patients and is related to systemic inflammatory response. Lung cancer patients need a comprehensive care including evaluation of fatigue and weakness.

Keywords: Fatigue, lung cancer, systemic inflammation, muscle weakness

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INTRODUCTION

Fatigue is increasingly recognized as a troublesome problem in patients with cancer.[1] Assessment of cancer-related fatigue (CRF) is challenging as there is no commonly agreed definition of this symptom. One definition describes fatigue as "a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest".[2] As indicated by this definition, fatigue is a subjective phenomenon and thus self-report measures are currently the gold standard for fatigue assessment. Numerous instruments are used to assess cancer-related fatigue, including items and subscales from mood and quality of life measures as well as multidimensional scales that were developed and validated specifically for cancer patients.

The majority of patients with advanced cancer experience fatigue; its prevalence has been estimated to vary between 33% and 100% depending upon the assessment instrument used and the population studied.[3] Most of the previous studies were on patients with breast carcinoma or with various solid tumors, with few studies on lung carcinoma. However, the prevalence of fatigue seems to be higher in lung cancer patients: 50% among patients with inoperable non small cell lung cancer as compared to 16% among patients with recently diagnosed prostate cancer and 15% among patients with recently diagnosed breast cancer; and was reported to be as high as 78% among patients receiving specialist inpatient palliative care.[3]

Qualitative reports suggest that cancer-related fatigue differs from "normal" fatigue due to lack of sleep or overexertion as it is more severe, longer lasting, and is not relieved by adequate sleep or rest.[4] Fatigue has a detrimental impact on all aspects of quality of life among both cancer patients and survivors. Over 50% of cancer patients reported that fatigue affected their ability to work, their physical and emotional well-being, their social activity, and their ability to enjoy life.[5] Increased fatigue may also be related to poorer survival.[6] However, despite the importance of fatigue, little is known about which factors are important in determining the severity of fatigue in patients with advanced cancer. The etiology is often unclear, and multiple etiologic factors for fatigue may coexist. Potential factors contributing to fatigue may be the cancer itself, cancer treatment, cancer or treatment complications, medications, and other physical and psychosocial conditions.[7] It has been described as a major complication of chemotherapy, radiotherapy and biological therapies.[3] Fatigue has also been reported to be related to anemia and loss of weight, particularly loss of muscle bulk.[8] Loss of lean tissue, anemia, poor performance status, and fatigue severity has been associated with the systemic inflammatory response in patients with advanced cancer.[8]

Experimental studies suggest that increases in inflammatory marker levels might be responsible for fatigue in cancer patients.[9] Animal studies have shown that direct application of IL-1 into the brain leads to a variety of symptoms such as loss of appetite, fever and fatigue.[10] Besides, the parenteral application of high concentrations of recombinant proinflammatory cytokines such as IL-6, IL-12, IL-1β, TNF-α to enhance immune defenses against cancer often leads to a syndrome referred to as the systemic inflammatory response syndrome. One of the major symptoms of this systemic response is intense fatigue, which in many patients calls for dose reduction or even interruption of therapy.[11] This converging evidence suggests that fatigue in cancer patients is associated with a persistent activation of the immune system and an increased production of inflammatory markers.

Although fatigue is a commonly experienced symptom by patients with advanced lung cancer, adequate studies with control groups has not been done on the correlates of fatigue in this population. The aim of this study was, therefore, to investigate the correlates of fatigue and weakness in advanced-stage non-small cell lung cancer patients.

MATERIAL AND METHODS

Subjects

Sixty-three male lung cancer patients (mean age 65.63±9.87 years) were admitted to the study consecutively. All patients were histopathologically confirmed to have NSCLC. None of the patients had undergone surgical resection, or had received chemotherapy or radiotherapy at the time of sampling. Twenty-five age and sex-matched volunteers were admitted as the control group. Subjects with comorbidities that may cause fatigue or leading to systemic inflammation (diabetes, alcholism, malabsorbtion, cardiovascular, renal, hepatic diseases, infection, COPD, collagen vascular diseases) were excluded from the study.

Staging of the NSCLC patients was established by clinical findings, chest X-ray, bronchoscopy, computerized tomograophy (CT) of thorax, cranial magnetic resonance (MR) and positron emission tomography-computed tomography (PET-CT) on the basis of the latest TNM staging system (12). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

The study was approved by the institutional ethics committee and all subjects gave written consent to participate in the study.

Laboratory Tests

Fasting blood samples were collected for routine laboratory analysis of nutritional parameters, thyroid hormones, testosterone, cortisol and acute phase reactants (APR) at 8.00-10.00 A.M. Serum C-reactive protein (CRP) concentration (mg/L) was measured by a commercially available kit using a

turbidimetric method (Tokyo Boeiki, Prestige 24i, kit no: 81067HWOO, Tokyo, Japan).

Assessment of Fatigue and Weakness

The fatigue scores of the subjects were evaluated by "3-item fatigue subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30" (EORTC QLQ-C30).[13] The three questions "Did you need to rest?", "Have you felt weak?", and "Were you tired?" were asked to the subjects and how true each question had been over the previous week were scored between 1 (not at all) and 4 (very much). The total score for the 3 questions was transformed into a 0–100 scale using a scoring algorithm. High scores represented high levels of fatigue.[14]

A simple 10-cm visual analogue scale ranging from "I don't feel weak at all" to "I couldn't feel any weaker" was used as a measure of weakness. Subjects were asked to mark the line at a point that they felt represented best how they were feeling currently.[8] While the other questionnaires inquired about symptoms in the previous week, the VAS specifically concerned symptoms experienced at the time of their completion. Higher scores represented a worse level of symptoms.[14]

Statistical Analysis

Statistical tests were done with the SPSS software program. Results were presented as mean ± SD. Correlations between parameters were evaluated using the Spearman's rank correlation coefficient. Non-parametric data of study groups were compared by Mann-Whitney U test. A p value of ≤ 0.05 was taken as statistically significant.

RESULTS

Demographic data of study groups and tumor characteristics of NSCLC patients admitted to the study are shown in **Table I**. The study groups were age and sex-matched; they were all male and the mean age was 65.63±9.87 in NSCLC group and 63.52±11.54 in the control group. The cigarette-burden of the groups was similar (p=0.079). 43% of NSCLC patients were classified as stage III cases and 57% as stage IV cases. Histological subtypes were squamous cell carcinoma in 17.5%, adenocarcinoma in 23.8% and unspecified NSCLC in 58.7% of the patients. BMI of NSCLC group was lower than controls (p=0.026).

Nutritional parameters, acute phase reactants, hormones, fatigue and weakness scores of NSCLC patients and controls are shown in **Table II**. Hemoglobin and other nutritional parameters were lower in cancer patients. The positive acute phase reactants CRP, leucocyte, ferritin, thrombocyte and fibrinogen levels of NSCLC group were higher than controls. Serum albumin (which is a negative APR) was lower in cancer group whereas there was no difference in transferrin level. Results of the hormonal analyses revealed difference in TSH

Table I. Demographic data of study groups and tumor characteristics of NSCLC patients

	NSCLC (n=63)	Controls (n=25)	p
Age (year)	65.63±9.87	63.52±11.54	0.063
Gender M/F (%)	100	100	–
Smoking (pack-year)	63.84±30.29	60.72±27.34	0.079
Weight loss, n (%)	33 (52.4)	0	–
BMI (kg/m^2)	23.51±4.58	27.76±3.90	0.026
Stage, n (%)			
IIIa-IIIb	27 (43%)	–	–
IVa-IVb	36 (57%)	–	–
Histologic subtypes, n (%)			
Squamous cell	11 (17.5%)	–	–
Adenocarcinoma	15 (23.8%)	–	–
NSCLC (unspecified)	37 (58.7%)	–	–

NSCLC: Non-small cell lung carcinoma; BMI: Body mass index

Table II. Demographic data of study groups and tumor characteristics of NSCLC patients

	NSCLC (n=63)	Controls (n=25)	p
Nutritional parameters			
Hemoglobin (g/dL)	12±1	14±1	<0.001
Lymphocyte (mkrL)	1952±922	2404±806	0.028
Cholesterol (mg/dL)	160±39	205±30	<0.001
Hormones			
TSH (μIU/mL)	0.51±0.52	1.04±0.79	0.001
fT3 (pg/mL)	3.01±1.06	3.57±1.08	0.041
fT4 (ng/dL)	1.45±0.93	1.20±0.23	0.067
Testosterone (ng/mL)	304±174	434±146	0.002
Cortisol (μg/dL)	15±15	18±9	0.113
Acute phase reactants			
CRP (mg/L)	44±36	6±14	<0.001
Leucocyte (mkrL)	9815±3166	8442±1923	0.042
Thrombocyte (mkrL)	368936±134528	243952±104813	<0.001
Ferritin (ng/mL)	252±212	110±86	0.009
Fibrinogen (mg/dL)	436±158	240±93	<0.001
Albumin (g/dL)	4.26±0.49	4.68±0.41	<0.001
Transferrin (μg/dL)	178±51	190±38	0.339
Fatigue&weakness scores			
EORTC QLQ-C30 fatigue score	65.14±26.52	12.28±4.56	<0.001
VAS weakness (cm)	5.76±2.34	1.21±0.48	<0.001

NSCLC: Non-small cell lung carcinoma; TSH: Thyroid-stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine; CRP: C-reactive protein; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire C30; VAS: Visual analogue scale

(thyroid stimulating hormone), fT3 (free triiodothyronine) and testosterone levels of the lung cancer patients and controls; they were all lower in the cancer group, whereas there was no difference in cortisol levels. Fatigue and weakness scores of the cancer patients were significantly higher than controls.

Correlates of fatigue and weakness in NSCLC patients are given in **Table III**. In correlation tests, fatigue score was positively correlated with weakness score, stage of the cancer, leucocyte and thrombocyte counts; and was negatively correlated with BMI, hemoglobin, fT3, albumin and transferrin levels. Weakness score was positively correlated with stage of the cancer and negatively correlated with fT3, albumin and transferrin in NCSLC patients. Circulating CRP concentration was positively correlated with both fatigue score and weakness score. Fatigue and weakness scores were not correlated with age, cigarette-burden, and the circulating lymphocyte, cholesterol, ferritin, fibrinogen, testosterone and cortisol levels of the patients.

DISCUSSION

Cancer-related fatigue (CRF) is a very common and distressing condition, and was reported to have a considerable impact on various aspects of patients' quality of life. Areas particularly affected were the ability to work, the ability to enjoy life and patients' sex lives. Therefore, research into the etiology and management of this symptom should be regarded as a priority.

Table III. Correlates of fatigue and weakness in NSCLC patients

	r	p
Fatigue score &		
weakness score	0.789	0.000
stage	0.297	0.019
leucocyte	0.291	0.022
thrombocyte	0.305	0.016
BMI	-0.268	0.036
hemoglobin	-0.346	0.006
albumin	-0.415	0.001
transferrin	-0.444	0.001
fT3	-0.0331	0.015
CRP	0.411	0.001
Weakness score &		
stage	0.425	0.001
albumin	-0.392	0.002
transferrin	-0.401	0.004
fT3	-0.297	0.031
CRP	0.256	0.044

BMI: Body mass index; fT3: free triiodothyronine; CRP: C-reactive protein

CRF is now seen as more troublesome to cancer patients than cancer-related pain, nausea or vomiting. Patients with cancer felt that fatigue adversely affected their daily lives more than pain (61% vs. 19%).[1] Fatigue affected 58% of cancer patients whereas the comparable figure for nausea/vomiting was 18%.[15] Despite this high prevalence, fatigue had never been reported to the hospital doctor by 52% of the patients with this symptom and only 14% had received treatment or advice about the management of their fatigue.[15]

Stone et al reported the prevalence of 'severe subjective fatigue' (defined as fatigue greater than that experienced by 95% of the control group) as 75%. EORTC fatigue score was 67 (0–100) and VAS weakness score 6.15 cm in their study on inpatients with advanced solid cancer whereas they were 11 and 0.4, respectively, in the control subjects.[14] Similarly, in the present study the mean group fatigue and weakness scores were significantly higher in the lung cancer patients as compared to the controls, , i.e 65 versus 12 and 5.76 cm versus 1.21 cm, respectively.

If cancer patients do experience more fatigue than the general population, then what is its cause? Fatigue may be due to the underlying cancer itself, in which case one might expect that different cancers would have different fatigue-inducing effects. Fatigue was found to be highest in patients with lung cancer and lowest in patients with gynecological cancers.[3] Physical fatigue was also significantly correlated with stage of disease. The highest level was in metastatic disease, followed by localised disease and disease in remission.[3] In the present study, we found a significant positive association between fatigue severity and disease burden in lung cancer patients; fatigue and weakness scores increased as the stage increased. Although some relationship appears to exist between cancer-related fatigue and the type and stage of malignancy, these factors alone can not explain most of the variation in fatigue between individuals.

Obviously, fatigue is a multidimensional symptom that is likely influenced by multiple factors that coexist and vary in influence depending on individual characteristics of the patient. Psychosocial factors are strongly correlated with fatigue, including depression, anxiety, and coping style.[16] Demographic factors, physical symptoms, and comorbid medical conditions have also been identified as correlates of fatigue.[16,17] Although there is much speculation about the role of biological factors in CRF, empirical research has been limited. Indeed, among the biological parameters evaluated to date (i.e., hemoglobin, albumin, thyroid hormones), none fully account for fatigue during or after cancer treatment. Cachexia, abnormal muscle functioning, anemia, physical deconditioning, psychological distress or the severity of other symptoms have all been suggested at one time or another as possible causes for CRF.[17] Recently, there is growing interest in the role of proinflammatory cytokines and the cytokine network in CRF.[17]

During the last decade, the links between illness-related psychological symptoms such as fatigue and ongoing inflammatory processes have received increasing attention in cancer research. Suffering from cancer and being treated for cancer are related to the release of inflammatory markers and the expression of receptors for inflammatory markers both by immune cells and malignant cells.[9] Several lines of evidence suggest that increases in inflammatory marker levels might be responsible for fatigue in cancer patients. Alexander et al investigated the prevalence of CRF in a population of breast cancer survivors and found that total white cell count and CRP were significantly higher in the cases of CRF.[18] A previous meta analysis has found evidence of an association between CRF and circulating systemic inflammatory markers (IL-6, IL-1ra and neopterin) in cancer patients.[9] Orre et al investigated circulating levels of various inflammatory markers in long-term survivors of testicular cancer and found higher levels of IL-1ra and CRP in cases compared to controls and concluded that the findings lend some support to the hypothesis that low-grade inflammatory processes are involved in the pathogenesis of chronic cancer-related fatigue in cancer

survivors.[19] In support of such an association we did find a significant correlation between fatigue and weakness scores and markers of systemic inflammation in our study. We established that the fatigue score was positively correlated with positive APR (leucocyte and thrombocyte counts); and was negatively correlated with negative APR (albumin and transferrin levels). Weakness score was also negatively correlated with albumin and transferrin in NCSLC patients. Moreover, circulating CRP concentration was positively correlated with both fatigue and weakness scores.

Fatigue is often assumed to be related to poor nutritional status.[20] Cachectic patients frequently have decreased muscle bulk and this might be expected to lead to physical weakness and easy fatigability. Moreover, some authors have reported abnormal muscle electrophysiology in cancer patients even in the absence of cachexia.[21] However no study has yet demonstrated that these changes in muscle function are associated with increases in subjective fatigue. The exact mechanisms of cancer cachexia remain unclear, but are almost certainly multifactorial. Development of cancer cachexia is related to a large degree to a chronic, low-grade, tumor-induced activation of the host immune system. The systemic inflammatory response, as evidenced by elevated circulating concentrations of acute phase proteins including CRP and cytokines including TNF-α, is shown to be an important factor in the progressive nutritional decline of these patients.[22,23] As a matter of fact, weight loss and fatigue are said to form a clinical syndrome of 'anorexia-cachexia asthenia'.[24] In our study, nutritional parameters and BMI were lower in cancer patients than controls and the fatigue score was negatively correlated with BMI and albumin.

Hemoglobin levels were lower in our lung cancer patients and we found a negative correlation between hemoglobin and fatigue score. Fatigue in cancer patients is often attributed to anemia, but the relationship between hemoglobin level and fatigue among such patients is not well understood. Stone et al found a weak but significant association between hemoglobin level and fatigue, but hemoglobin levels were not independently predictive of fatigue when a multivariate analysis was undertaken.[3] However, it is possible that fatigue may be more related to changes in hemoglobin level than to any particular hematocrit. In support of this, studies of anemic patients receiving erythropoietin therapy have reported that increases in hematocrit are associated with improvements in fatigue.[25]

Alterations in thyroid function tests are common in critical illness and also in chronic, systemic diseases including cancer.[26] Frequently detected abnormalities of thyroid function in non-thyroidal illness syndrome (NTIS) are decreased total triiodothyronine (TT3) and free triiodothyronine (fT3), normal or decreased total thyroxine (TT4) and free thyroxine (fT4). Despite these changes, serum thyroid-stimulating hormone (TSH) does not increase and can even be decreased.[27] TSH and fT3 were lower in our lung cancer patients and fatigue/weakness scores were negatively correlated with fT3. These results are compatible with NTIS which is probably another consequence of the cancer-related systemic inflammation.

Since none of our NSCLC patients had undergone surgical resection, or had received chemotherapy or radiotherapy at the time of sampling, we can conclude that their fatigue was not related to treatment or treatment complications.

Fatigue is a difficult symptom to study in any group of patients but particularly in those with advanced cancer. Physicians are usually focused on symptoms like pain, nausea, dyspnea, weight loss in cancer patients but fatigue, which is a very frequent symptom worsening quality of life especially on late stages of the disease, is usually overlooked. However, patients with advanced lung cancer need a comprehensive care including evaluation of fatigue and weakness. The research methodology used in this study was found to be both practical in even very sick patients and may be used in routine clinical evaluation of lung cancer patients.

The present study was able to identify a number of factors that were significantly correlated with fatigue severity. Fatigue is a prominent symptom in advanced NSCLC patients and related to cancer-related systemic inflammatory response. Recognizing the extent and severity of this symptom in advanced cancer will be the first step towards improving its management in the future. Besides, research on inflammation and cancer-related fatigue will elucidate the biological basis for this common and troublesome symptom and may also promote the development of targeted therapies.

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Disclosures

None

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