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Chronic fatigue in adult cancer survivors

CLINICAL REVIEW

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Pronounced fatigue including tiredness and lack of energy are common both during and after cancer treatment. Between 15–35 % of adult cancer survivors experience chronic fatigue. Chronic fatigue has a negative impact on affected individuals' social, occupational and general functioning, and may lead to a considerably reduced quality of life.

Pronounced tiredness, exhaustion and lack of energy are among the most common symptoms during oncological treatment (1–3). In most cases, this tiredness will gradually disappear after treatment cessation, but not everyone experiences improvement. Up to 35 % of those who have completed curative treatment, and who are without known cancer, will experience persistent tiredness after completion of treatment (3,4). Other cancer survivors may experience a brief period of time without this symptom after treatment completion, but later on feel declining energy levels.

Chronic fatigue is defined by elevated levels of fatigue and/or impaired memory and concentration lasting for six months or more (5). For most of those affected, chronic fatigue has a negative impact on everyday functioning and work capacity, and may lead to considerably reduced quality of life (3).

Cancer-related fatigue is not a diagnosis in ICD 10, and there are no established criteria to classify cancer-related fatigue as a separate condition. Cancer-related fatigue can be defined as a subjective feeling of tiredness, weakness or lack of energy (6) or as an exhausting, persistent subjective sense of physical, emotional and/or cognitive tiredness that is disproportionate to the level of activity (7,8). Even though fatigue is also a cardinal symptom of myalgic encephalomyelitis (ME), ME is defined by the presence of additional symptoms, e.g. musculoskeletal pains, gastrointestinal complaints and/or tender lymph nodes (9). 'Chemobrain' (chemotherapy-related cognitive dysfunction) is most often used to describe chemotherapy-induced cognitive dysfunction. Even though the symptoms can overlap those of mental exhaustion, it is not known whether they represent the same or two different conditions.

This article concerns chronic fatigue in survivors treated for cancer as adults (> 18 years). The aim of the article is to inform health personnel who meet adult cancer survivors about the prevalence of chronic fatigue, associated factors, screening and possible interventions.

Method

The article is based on international guidelines for evaluating chronic fatigue in adult cancer survivors (7,8,10), a subjective selection of the relevant literature, and the authors' own clinical experience and research.

Measurement and prevalence

Various questionnaires have been used to study the prevalence of fatigue after cancer treatment (11), making it difficult to compare the results of different studies. The Fatigue Questionnaire (FQ) measures the level of physical and mental tiredness as well as the duration of the complaints (5). This questionnaire is therefore recommended for multi-dimensional mapping of chronic fatigue in cancer survivors (11).

This questionnaire was also used to investigate the prevalence of chronic fatigue in the Norwegian general population in the 1990s. At that time, the prevalence of chronic fatigue was 13 % for women and 10 % for men, and showed a modest increase with increasing age (12). The sensitivity of the Fatigue Questionnaire to assess change in fatigue over time has

not been clarified. In studies aiming to measure this, the use of other instruments should be considered. In clinical practice, a simple numerical scale from 0 (no tiredness) to 10 (worst possible tiredness) can help to map the severity of symptoms and highlight changes (7).

Chronic fatigue is one of the most prevalent late effects in adult cancer survivors. Norwegian studies have shown that 25–35 % of long-term survivors of breast cancer, lymphoma and cervical cancer are affected by chronic fatigue (4), (13–15), and that 26 % and 13 % of hormone-naïve men reported chronic fatigue two years after radical radiotherapy and radical prostatectomy for prostate cancer, respectively (16). Recently it was demonstrated that the prevalence of chronic fatigue in Norwegian testicular cancer survivors increased from 15 % twelve years after treatment to 27 % seven years later (17).

Fatigue is also a frequent problem among other groups of cancer survivors, for example prevalences of over 40 % are reported for survivors of colorectal cancer and lung cancer (18–20). However, the prevalence of chronic fatigue in these groups is unknown as the duration of the fatigue symptoms was not measured. Even though chronic fatigue has been studied in other groups of cancer survivors, the prevalence of chronic fatigue in these groups is not definitely known due to the small number of studies and varying methodology used.

Associated factors

Earlier data have not consistently shown a correlation between the development of chronic fatigue and the type or intensity of cancer treatment (21–23). Recently, however, a meta-analysis showed that the risk of severe fatigue among breast cancer survivors increased after combined treatment with surgery, chemotherapy and radiotherapy compared with surgery or surgery and radiotherapy alone (24). Radiotherapy has also been discussed as a possible aetiological factor for the development of chronic fatigue in prostate cancer survivors (16).

There is broad agreement that chronic fatigue among cancer survivors cannot be explained only by disease- and treatment-related factors, and that chronic fatigue is a multifactorial phenomenon that is affected by somatic, demographic and psychosocial factors (3). Also in the general Norwegian population, sociodemographic and health-related factors were associated with chronic fatigue (12). Living alone, having a low income or experiencing psychological discomfort such as anxiety, pessimism and low mood/depression are associated with chronic fatigue in cancer survivors (3,15).

Comorbid conditions or other late effects and symptoms such as cardiovascular disease, pulmonary disease, overweight, sleep disturbance, hormonal changes, peripheral neuropathy, and persistent pain may also be contributory factors (3,13,14,16,17).

In recent years, attention has been paid to perpetuating factors, in particular physical inactivity and catastrophizing as a psychological response to fatigue (3). Several biological mechanisms have been studied as possible underlying causal factors, including changes in the hypothalamic-pituitary-adrenal axis such as dysregulation of glucocorticoid production and/or glucocorticoid receptors, and altered ATP and muscle metabolism. Of the biological mechanisms, the main focus in recent years has been on inflammation as a cause of chronic fatigue, in particular on dysregulation of cytokines and proinflammatory cytokines, although findings are not conclusive (3). The inflammation hypothesis is supported by relatively consistent findings on a correlation between fever, weight loss and night sweats (B symptoms), and chronic fatigue in lymphoma survivors. A possible explanation for radiotherapy as an aetiological factor for developing chronic fatigue in prostate cancer survivors may be that such treatment more than surgery can induce long-lasting inflammatory processes (16).

Screening and assessment

The evidence for what constitutes optimal screening of individuals with chronic fatigue after cancer treatment is weak (7). Assessment must therefore be based on clinical judgment and the presence of risk factors and other factors that can contribute to perpetuating and/or increasing symptoms in the individual patient. Possible recurrence of the cancer should always be considered, especially if a patient who has felt well develops fatigue.

Based on international guidelines and the Norwegian Directorate of Health's recommendations in the publication *Seneffekter etter kreft* (Post-cancer treatment effects), factors useful to assess in cancer survivors affected by this symptom are presented in the box below (Box 1).

Box 1 Suggestions for screening of chronic fatigue in adult cancer survivors. The overview is based on international guidelines and the Norwegian Directorate of Health's recommendations (7, 8, 25)

Assessment of fatigue level (Fatigue Questionnaire or similar questionnaires)

General history of fatigue: onset, pattern, duration, change over time, factors that exacerbate/improve the symptoms, pattern of activity throughout the day and week

Other factors:

- psychological factors, particularly high anxiety level and catastrophising sleep, pain, medication, abuse of alcohol or narcotics
- somatic comorbidity
- cancer treatment can predispose for comorbidity, for example cardiomyopathy after cardiotoxic chemotherapy or hypothyreosis following radiotherapy targeting the lower neck

A general physical examination should be undertaken to detect somatic conditions as an underlying cause. Recurrence of the cancer should be considered if a patient who has been in good shape develops fatigue

Additional examinations must be considered individually:

- Relevant blood tests are: haematological profile, hormone tests (including thyroid status), electrolytes, liver/gallbladder function
- Radiological examinations should be performed if clinical signs of somatic disease
- Referral to other medical specialists must be based on findings and clinical evaluation. Referral to the following may be needed:
 - Cardiologist after completion of cardiotoxic treatment
 - Neuropsychologist in cases of memory and/or concentration difficulties, particularly in younger patients
 - Psychologist/psychiatrist if signs of mental disorders
 - Pain management team
 - Endocrine evaluation

Interventions

One's approach and guidance to someone who is struggling with chronic fatigue after cancer treatment must be based on clinical experience and tailored to the individual. If the screening indicates somatic or mental conditions in need of treatment, such therapy must be provided. There is otherwise no specific treatment for chronic fatigue, but there are several interventions that can alleviate the symptom (26).

It is generally recommended that the patient should receive updated information about chronic fatigue and about contributory and remedial factors. Advice on activity pattern is often useful because many patients exaggerate their activity level on good days resulting in exhaustion for several days after, which in turn may lead to a reduction or at worst a gradual decline in physical activity over time. Advice on energy conservation by adjusting activity levels to one's perceived level of energy might also be helpful to avoid fluctuations, and possibly help to gradually increase physical capacity. For all those affected it is recommended to maintain a regular circadian rhythm and to avoid sleeping during daytime (7,8).

Other interventions fall into three main categories: physical activity, cognitive therapy and stress-reducing therapies. A recently published meta-analysis showed that physical activity and psychological interventions improve chronic fatigue to almost the same extent. The effect was equal regarding anaerobic and aerobic exercise, while cognitive therapy was the most efficacious of the psychological interventions. All interventions had best effect in a group setting (26).

Even though chronic fatigue can be a dynamic condition, there are no data that specifically indicate how many can be expected to recover after physical training/cognitive therapy. Yoga, acupuncture and mindfulness-based approaches have also shown promising results in some studies (7,27). Currently, however, no general recommendations can be given since these studies are few, with only a limited number of patients included and with a lack of data on the duration of the effect.

Without verifiable documentation, aspects of the case history and symptoms may nevertheless indicate the best approach for the individual patient. For someone who is physically inactive, physical activity after consulting their physician may be a good first choice. For those with a tendency to catastrophize and with dysfunctional thoughts, cognitive therapy may be the best choice, while stress-alleviating interventions may be best for those with high anxiety and stress levels.

Regular physical activity has been documented as an effective intervention (28). It has not been clarified what intensity and type of physical activity is most effective. However, in our experience an individualised programme with a gentle start and gradual progression is important, and so far the literature also supports this. Many patients want to start at a too high intensity which may result in training interruptions, or at worst exacerbation of the fatigue. For most cancer survivors with chronic fatigue, a moderately intense training programme, including brisk walking, cycling and/or swimming will be safe (7). If the patient has other post-cancer late effects (cardiac affection, polyneuropathy) or comorbid conditions, his/her training programme must be adjusted according to this.

The above meta-analysis describes physical activity as seemingly most effective during ongoing cancer treatment, while psychological interventions – or a combination of physical training and psychological interventions – may be best for cancer survivors (26).

Numerous rehabilitation programmes are available for patients with chronic fatigue. Additionally, courses on learning to cope are arranged for patients at some learning and coping centres and the Varde centres (centres for cancer patients and their families established at some hospitals by the Norwegian Cancer Society and the regional health authorities). Psychostimulants (methylphenidate and modafinil) have been used in other countries but are not offered to patients in Norway due to lack of documented effect.

All health personnel who meet cancer survivors should have knowledge about chronic fatigue and interventions that can alleviate the symptom. Even though some cancer survivors receive follow-up care from a surgeon or oncologist, it will mostly be GPs who meet cancer survivors suffering from chronic fatigue. The GP can contribute by giving the patient information about the condition and possible interventions such as energy conservation, physical activity and cognitive therapy. The GP will also have knowledge about comorbidity and risk factors for the individual patient. Moreover, the GP will be of

key importance in the administration of social security agreements so that the patient can cope with his/her occupational situation. Therefore, screening and monitoring of these patients should primarily be the GP's responsibility.

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