Fatigue

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Fatigue is today the most common and incapacitating side effect in patients with cancer. Fatigue affects both physical and psychosocial function and reduces the patients' quality of life. It is aggravated with co-morbidities and the presence and severity of other symptoms like pain, insomnia, depression, anxiety, diarrhoea. Risk factors also include female gender and young age. The mechanisms explaining fatigue is still mostly unknown and there is no general treatment to alleviate the symptoms, although effective treatment of co-existing symptoms and easy exercise will make some benefit. The multidimensional syndrome fatigue has a profound effect on the patients' quality of life, including the physical, psychological, and economic/occupational aspects. The objectives of the article are further to describe the causes and contributing factors for fatigue, tentative mechanisms of action and treatment.[1]

Patients with severe diseases such as cancer commonly report tiredness or a lack of energy during the course of their disease and treatment,[2] which is not equivalent to anything they have experienced before the advent of their illness. This syndrome, called fatigue, is long lasting and interferes with every aspect of life.[3] The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as 'a persistent, subjective sense of tiredness related to cancer or cancer treatments that interferes with usual functioning'.[4 5] It differs from the fatigue of everyday life, which usually is temporary and is relived by rest. CRF is more severe, more distressing and usually not relieved by rest.[5]

CRF is a multidimensional syndrome. There are different symptoms and concepts of CRF, such as decreased activity, muscle weakness, lack of mental alertness and lack of energy.[5] Severe CRF has a number of major contributing factors, including cachexia, depression, pain, treatment with opioids and other medications, anaemia, different antineoplastic treatments and loss of fitness. Some contributing factors, such as anaemia and medications, may occasionally be corrected, but there is no specific remedy for most factors that contribute to CRF.[1 5]

The majority of CRF studies have been conducted on patients with cancer receiving cytotoxic drug treatment. It is suggested that the prevalence of fatigue related to administration of cytotoxic drugs may be 75–100%.[4–6] Despite the obvious relevance of the phenomenon, fatigue has either not been recognised or has been overlooked while clinicians get better control over the more acute symptoms of nausea, emesis and pain.[4 5]

MECHANISMS CAUSING FATIGUE

Both an underlying disease and treatment may cause fatigue and they are hard to separate since they coexist. Many factors may contribute to subjective fatigue,[4 5] and the exact mechanisms are not completely known. The contribution of each factor may vary between patients and in individual patients over the course of illness and treatment. The degree of fatigue might also differ among diseases.[7 8]

Proposed mechanisms to explain fatigue include abnormalities in the periphery in energy metabolism related to increased requirements, for example, due to infection, fever or surgery; decreased availability of metabolic substrates, for example, due to anaemia, hypoxaemia or poor nutrition. Fatigue may also be due to the abnormal production of substances that impair metabolism or normal muscle function, for example, cytokines or antibodies. Other proposed mechanisms link fatigue to the pathophysiology of central functions such as sleep disorders and major depression.

Fatigue may cause 'stress' and alterations of several neurotransmitter systems in the brain. The transmitter systems usually discussed are the serotonergic and noradrenergic systems. Both these systems are closely linked to the control of corticotropine-releasing hormone (CRH) release and hence patients with fatigue have increased CRH sensitivity. Low brain concentrations of serotonin, norepinephrine and dopamine, but also an activated hypothalamic–pituitary–adrenal (HPA) axis, are linked to elevated glucocorticoid concentrations.[1 9]

Cytokines are released in many diseases and during treatment. Of these, interleukin (IL)-1β, IL-2 and IL-6 have been of particular interest. ILs activate the hypothalamus–pituitary axis which controls CRH release,[10] and is closely linked to serotonergic and noradrenergic neurotransmission. A close link between serotonin (5-hydroxytryptophan (5-HT)) and tumour necrosis factor α (TNFα) has been established and TNFα may change the serotonin metabolism by increasing the neuronal release of 5-HT. An increase in transport of 5-HT is seen, which thereby decreases the level of 5-HT in the synaptic space. This feedback loop between 5-HT and TNFα can be dysfunctional in the case of increased cytokine release due to cancer treatment. An increase in HPA axis function also leads to increased levels of cortisol, which in turn is controlled by the interaction of 5-HT with the HPA axis.[11 12]

Drug treatment may cause fatigue either directly or indirectly. It may contribute directly by suppressing bone marrow or kidney function, thus causing hypoproliferative anaemia. Indirectly, cytotoxic drug treatment may have an effect on cytokines at the cellular level, peripheral neuromuscular junctions or the central nervous system.[1 3] In patients receiving cyclic cytotoxic drug treatment fatigue often peaks within a few days and declines until the next treatment cycle.[1 5 13]

MANAGEMENT OF FATIGUE

The limited knowledge about the mechanisms of CRF has led to a lack of efficient treatment of fatigue and inappropriate treatment.[5 14 15]

The NCCN expert panel has drawn up guidelines on the diagnostic evaluation and treatment of patients with CRF in a cyclical approach: screening, primary evaluation, interventions and re-evaluation. They also proposed: 'Seven primary clinical conditions (pain, emotional distress, sleep disturbance, anaemia, nutrition, activity level and other co-morbidity) associated with fatigue should be evaluated individually'.[5]

The first essential step is to give patients adequate information. Second, patients should be educated to manage fatigue.[5] With appropriate support, patients may be prepared for side effects and adopt management strategies.[6] Unfortunately, a recent survey indicates that fatigue is seldom discussed by patients and their nurses or physicians.[13]

If a specific cause of fatigue is identified, such as anaemia, insomnia, depression, metabolic disorder etc, then this should be treated first.[5] The contribution of each factor may vary between patients and in individual patients.

There is a lack of efficient treatment of fatigue and inappropriate treatment have

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been tried, most frequently based on dietary and vitamin support, in some cases pharmacological treatment and in others complete rest.[5] The pharmacological therapies tested to combat fatigue have not been rigorously evaluated in controlled trials. Nonetheless, there is evidence to support the use of several classes of drug.[6 13]

Exercise, modification of activity, assessment of sleep patterns, stress management and cognitive therapies, adequate nutrition and hydration are all non-pharmacologic methods of dealing with fatigue.[10] In recent years, scientific evidence has dramatically changed the ideas about the relationship between physical activity, rest and fatigue.[16] Convincing clinical evidence supports the management of fatigue with physical exercise.[1 17–22]

CONCLUSION

Fatigue is a debilitating and severe symptom that may affect more than 90% of patients with certain diseases and undergoing certain treatments. It is now overshadowing pain and nausea/vomiting as the most feared symptom from cancer and cytotoxic drug treatment. Currently unconventional treatment paradigms like light exercise seem to be the most successful.

Many disorders and symptoms have a wealth of treatment alternatives. For others, there is a lack of treatment or poor treatment options and many patients have the challenge of dealing with the symptoms. We cannot only elaborate when we have good options; we need to close the gaps and to work across borders to reach those that do not have any treatment. We have to think right, and if possible share our experiences in *EJHP*.

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REFERENCES

1 Hartvig P. Fatigue—a challenging symptom for cancer patients treated with cytotoxic drugs—mechanisms and targets for treatment. *Ann Pharm Fr* 2010;68:76–81.
2 Curt GA, Breitbart W, Cella D, *et al*. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000;5:353–60.
3 Winningham ML, Barton-Burke M. *Fatigue in cancer. A multidimensional approach*. Chapter 8. Burlington, MA: Jones and Bartlett Publishers, 2000:153–69.
4 Ahlberg K, Ekman T, Gaston-Johansson F, *et al*. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003;362:640–50.
5 Stasi R, Abriani L, Beccaglia P, *et al*. Cancer-related fatigue. Evolving concepts in evaluation and treatment. *Cancer* 2003;98:1786–801.
6 Bruera E, Driver L, Barnes EA, *et al*. Patient-controlled methylphenidate for management of fatigue in patients with advanced cancer: a preliminary report. *J Clin Oncol* 2003;21:4439–43.
7 Aulin J, Wallenberg S, Wagenius G, *et al*. Physical exercise as treatment for cytotoxic drug induced fatigue 2004. *J Oncol Pharm Pract* 2006;12:183–91.
8 Hartvig P, Aulin J, Sahlin M, *et al*. Fatigue in cancer patients treated with cytotoxic drugs. *J Oncol Pharm Pract* 2006;12:155–64.
9 Geinitz H, Zimmermann FB, Stoll P, *et al*. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *Int J Radiat Oncol Biol Phys* 2001;51:691–8.
10 Steensberg A, Fisher CP, Keller C, *et al*. Il-6 increases IL-1ra, IL-10 and cortisol in humans. *Am J Physiol Endocrinol Metab* 2006;285:E434–7.
11 Larisch R, Klimke A, Mayoral F, *et al*. Disturbance of serotonin 5HT2 receptors in remitted patients suffering from hereditary depressive disorder. *Nuklearmedizin* 2001;40:19–34.
12 Bower JE, Ganz PA, Aziz N, *et al*. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* 2002;64:604–11.
13 Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 1999;4:1–10.
14 Berger A. Treating fatigue in cancer patients. *Oncologist* 2003;8:10–14.
15 Winningham ML. Strategies for managing cancer-related fatigue syndrome. *Cancer* 2001;92:988–97.
16 Morrow GR, Andrews PL, Hickok JT, *et al*. Fatigue associated with cancer and its treatment. *Support Care Cancer* 2002;10:389–98.
17 Dimeo FC. Effects of exercise on cancer-related fatigue. *Cancer* 2001;92:1689–93.
18 Dimeo F, Bertz H, Finke J, *et al*. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. *Bone Marrow Transplant* 1996;18:1157–60.
19 Dimeo FC, Tilmann MH, Bertz H, *et al*. Aerobic exercise in rehabilitation of cancer patients after high dose chemotheraphy and autologous peripheral stem cell transplantation. *Cancer* 1997;79:1717–22.
20 Dimeo FC, Stieglitz RD, Novelli-Fischer U, *et al*. Effects of physical activity on the fatigue and psychosocial status of cancer patients during chemotheraphy. *Cancer* 1999;85:2273–7.
21 Durak EP, Lilly PC. The application of exercise and wellness program for cancer patients: a preliminary outcomes report. *J Strength Cond Res* 1998;12:3–6.
22 Adamsen L, Midtgaard J, Rorth M, *et al*. Feasibility, physical capacity, and health benefits of a multidimensional exersise program for cancer patients undergoing chemotheraphy. *Support Care Cancer* 2003;11:707–16.