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Fatigue

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1. Introduction

1.1 The characteristics of fatigue

Many severely ill patients are afflicted with severe symptoms from both the disease and from treatment. The symptoms encompass not only physical incapacity but they also have a psychological impact, which seriously may hamper the daily living of the patient as well as the social situation (Curt et al., 2000). In cancer patients, pain and emesis is still a burden to the patients (Jacobsen et al., 1999; Patrick et al.,) although new treatment algorithms have been introduced that alleviates these symptoms so that fatigue at present is the most common and worst experienced symptom, afflicting up to 90 % of patients with cancer (Irvine et al, 1994.; Beam, & Richardson. 1996; Irvine et al, 1994; Hartvig et al., 2006a; Hartvig et al., 2006b). Fatigue is a French word with no absolute correspondence to English or many other languages. This symptom is distinct from typical tiredness experienced by healthy individuals as a result of normal daily life which is relieved by rest. Fatigue is described by the patients as a tiredness that *"is worse than they have ever experience before",* that makes them "*totally exhausted*" and *"unable to do even simple tasks"* (Curt et al., 2000).

Fatigue is a subjective multidimensional experience. It has various meanings in the scientific literature in which a common definition of fatigue is: "Fatigue is experienced as a subjective and internal feeling that appears not to be the same for everyone" (Ream & Richardson, 1996). According to the definition used by the National Comprehensive Cancer Network (NCCN) Fatigue Guidelines Committee, fatigue both refers to the physical and mental dimensions: "Fatigue is an unusual, persistent and subjective sense of tiredness related to e.g. cancer, or cancer treatment, that interferes with usual functioning" (Mock et al., 2000). Fatigue is associated with impairment of quality of life and thereby has a major impact on the patient, with significant consequences that may persist for a long period of time after completing treatment (Curt et al., 2000). Fatigue usually differs from excessive tiredness experienced by healthy individuals and is not relieved by rest or sleep.

Fatigue can be distinguished into mental and physical fatigue. The physical sensation of fatigue makes the patient unable to perform normal tasks due to the unusual feeling of tiredness. The mental fatigue could be experienced as emotional sensations e.g. decreased motivation, low mood and cognitive impairments and lack of concentration, respectively (Glaus et al., 1996; Ream & Richardson, 1997). The unusual character of cancer-related fatigue is described by a patient after therapy as: *"Now I feel just fine. That day I felt tired I did everything as I usually do, but every time I sat down, I only wanted to lie down and sleep"* (Adnan et al., 2010).

Fatigue can be acute or chronic. Acute fatigue is defined as intermittent, with rapid onset and only lasting for a short period of time (Wilson et al., 1994). Fatigue is perceived as chronic if it lasts for more than six months. Different studies have revealed that chronic fatigue may improve with time but that it mostly persists for many years (Wilson et al., 1994). This in turn has a major negative impact on the patients quality of life (Curt et al., 2000; Diaz et al., 2008). Several factors contribute to the experience of fatigue, and the influence and perception of each factor may vary from patient to patient, adding further complexity to the diagnosis. A lot of research has highlighted the correlation of physiological and psychological factors with the severity of fatigue (Hwang et al., 2003; Diaz et al., 2008). The mechanisms that cause fatigue in patients e.g. with cancer are not completely known but may be related to release of cytokines causing stress to the brain (Hartvig-Honoré., 2010).

1.2 Prevalence of fatigue as studied in cancer patients.

Fatigue seems to be a more frequent part of the symptom complex in certain types of cancer. Consistent among studies, lung cancer patients may experience the highest degree of fatigue (Richardson, 1995; Yennurajalingam et al., 2008). Patients with a diagnosis of prostate-, lymphoma- and gynecologic cancer stated that they experienced less fatigue before treatment for the cancer than during treatment (Hartvig et al., 2006a). For the gynecologic patients it was not expected that they were less tired during treatment than before, although they still experienced rather high degree of fatigue as a group. This result could be due to regression of their tumors. Women with breast cancer also reported fatigue before start of treatment (Jong et al., 2004). In compliance with this, other studies dealing with breast cancer patients undergoing adjuvant therapy have also found fatigue prevalent at baseline (Ancoli-Israel et al., 2006). There is large heterogeneity in fatigue in patients with gynecological cancers. It was noted that patients with ovarian cancer should be separated from patients with cervix cancer, since a study indicated that patients with ovarian cancer experienced a severe fatigue while patients with cervix cancer experienced less of fatigue (Piper, 1993). The perception of fatigue is also gender specific as it has been shown that women experienced higher degree of fatigue than men (Cella et al., 1998).

1.3 Cytotoxic drugs may aggravate fatigue

In an observational study on the evolution of fatigue during cytotoxic drug therapy, a rapid increase to the worst fatigue scores was most common for all patients on the second and third days after initiation of cytotoxic drug treatment. Close to hundred percent of the patients reported fatigue after the start of cytotoxic drug administration, a finding that was consistent across studies (Pater et al., 1997: Jacobsen et al., 1999). After an initial increase of fatigue for the first two days after administration start, it gradually declined until the next treatment (Hartvig et al., 2006a). A study investigating fatigue severity throughout three treatment cycles has shown that fatigue remained stable for 48 hours after each cycle (Andrykowski et al., 2005). The findings confirm that fatigue is a significant clinical problem during administration of adjuvant cytotoxic drugs for many cancer patients (Hartvig et al., 2006a; Adnan et al., 2010).

While there is strong evidence that fatigue is most common during treatment, studies have also found a substantial number of breast cancer patients suffering from persistent fatigue even after treatment completion. Jacobsen et al. (2007) suggest that fatigue is a major issue for

breast cancer patients becoming chronic in up to six months after completion of treatment. Another study showed an increased fatigue in up to 26% patients as compared to base-line levels post-treatment (Ancoli-Israel et al., 2006). This evidence confirmed that chemotherapy as a risk for developing fatigue that may continue long time even after treatment completion.

2. Contributing risk factors in cancer patients.

2.1 Type of cancer and treatment

There is a profound difference in the prevalence and severity in fatigue among cancer diagnoses as said. (Richardsson, 1995; Cella et al., 1998 ; Hartvig et al., 2006a; Hartvig et al., 2006b). This is both due to the cancer itself but also due to the cytotoxic drug regiment and to radiotherapy (Ahlberg et al., 2003) Breast cancer is the most studied patient population with large variations in severity due presence of contributing risk factors. (Jacobsen et al., 1997; Bower et al.; 2000).

2.2 Cytotoxic drugs

Analysis of cytotoxic drug regimens in an unselected group of patients revealed that the highest mean fatigue scores were experienced by patients from the first cycle who received in falling order: gemcitabine, cyclophosphamide, fluorouracil in combination, epirubicin (FEC), docetaxel, carboplatin and fluorouracil (Hartvig et al., 2006a; Hartvig et al., 2006b; Adnan et al., 2010). So far not any clear cut relationship between different cytotoxic drug regiments and the degree of fatigue has been truly established (Yennurajalingam et al., 2008). One study with a small number of patients in different treatment groups showed greater fatigue scores for subjects receiving bolus and continuous chemotherapy drugs as in the 5-flourouracil or the epirubicin, cisplatin and 5-fluorouracil protocol than for subjects receiving a short-term infusion every 21 days (Richardson et al., 1998).

2.3 Risk increase as co-morbidities, age and co-concomitant medicine

2.3.1 Kidney function

There are few studies that relate co-morbidities in patients to fatigue. In a study on hematologic malignancies, Kim et al. (2008) found that patients suffering from a kidney disease were more likely to report fatigue.

Studies have previously suggested that fatigue may be caused by elevated inflammatory activity. Additionally, kidney and hepatic function impairment could also be caused by inflammatory autoimmune disorders, which suggest a correlation between fatigue and impairment of kidney or hepatic function impairment. Another study on patients with haematological malignancies found that fatigue did neither correlate with inflammatory activities, nor with renal or hepatic function (Dimeo et al., 2004).

2.3.2 Age

Fatigue is more often and more severe in younger patients. Elderly women reported also less fatigue than the younger women did and young age is considered a risk factor for fatigue (Cella et al., 1998).

2.4 Co-related symptoms

Fatigue seems to be a most prominent and aggravating symptom experienced by a large majority of patients. Investigations carried out with heterogeneous groups of cancer patients (Hartvig et al., 2006a; Hartvig et al., 2006b) showed that fatigue appear to be one of the most frequently reported side effects. Evidence suggests that cancer-related fatigue is often accompanied by other bothersome adverse effects (Pud et al., 2008; Yamagishi et al., 2009).

A large scale research study was recently done identifying symptom prevalence and intensity in cancer patients receiving adjuvant chemotherapy (Jacobsen et al,. 1999). It was found that fatigue was one of the predominant symptoms occurring in cancer. Other disturbing symptom was reported and was ranged in severity in the following order: fatigue > sleep disturbance > unrest > anxiety > diarrhea > depression > constipation and pain.

2.4.1 Insomnia

Insomnia, e.g. sleep disturbance with difficulties falling asleep, disrupted sleep and early awakenings are common together with other sleep difficulties may often co-exist with fatigue. Among these insomnia and hypersomnia which are found affecting 30 to 50%, respectively of patients (Berger et al., 1998; Liu et al., 2009). Insomnia was also significantly associated with fatigue (Hwang et al., 2003).

Insomnia and subsequent sleep disturbances can lead to fatigue, mood disturbances, and contribute to Immuno-suppression, which can have a profound impact on quality of life and perhaps affect the course of disease. Insomnia in cancer patients must be distinguished from cancer-related fatigue (O´Donnel, 2004). Although they are two distinct conditions, insomnia and fatigue are interrelated. Insomnia often leads to daytime fatigue that interferes with normal functioning. Conversely, daytime fatigue can lead to behaviors such as napping, which results in insomnia. Because insomnia in this patient population may be due to a variety of causes, treatment must be multimodal and include both pharmacologic and non-pharmacologic therapies as discussed below.

Factors involved in circadian activities and rest have been evaluated and it was found that women who were less physically active and had increased number of night awaking reported higher cancer-related fatigue during chemotherapy (Andrykowski et al., 2005). In other words, sleep disorders may often exacerbate fatigue. The causal interrelationship between fatigue and sleep disturbance makes it difficult to distinguish between them. This is due to the fact that both sleep disturbance and fatigue might be a result of each other. Both symptoms are found to be most prevalent and most common during treatment of e.g. cancer patients. (Jong et al.. 2004). Women with cancer are even likely to experience fatigue and sleep disturbance before receiving their cytotoxic drug treatment (Jong et al., 2004).

2.4.2 Depression

Symptoms resembling fatigue are part of the associated symptom complex in patients suffering from fatigue. Therefore an association between depression and fatigue is common (Jacobsen et al., 1999). Depression experienced by severely ill as well as cancer patients is not significantly different from depression related to other diseases and medical conditions. However there is great variation in the reported frequencies of depression. A study assessed

depression during cytotoxic drug treatment, and it was found that patients suffer more from depression and other symptoms during treatment than before initiating treatment (Curt et al., 2000).

It is still unclear whether fatigue is a cause or a result of depression, as both symptoms are closely related (Jacobsen et al., 2007). A study examining the relation of cancer related symptoms and their co-occurrence on health related quality of life, found a 44% depression prevalence in out-patients with cancer (Hwang et al., 2003). An association between depression, anxiety and fatigue has been found (Jacobsen et al., 1999). This correlation was not maintained when fatigue increased.

2.4.3 Pain

Pain may also be a contributing factor to fatigue and affect adversely the quality of life. Cancer patients' experience of pain was found to be a major concern for most of them and had substantial impact on quality of life (Pud et al., 2008).

2.4.4 Emesis and nausea

Emesis and nausea are direct consequences of some treatment modalities. Just like pain, nausea and emesis are considered to be acute symptoms but manageable side effects that are most often palliated with antiemetic drugs. Studies have found that nausea and emesis contribute to fatigue severity (Diaz et al., 2008).

2.4.5 Anaemia

Anaemia may be a contributing factor to fatigue and so indirectly associated with an adverse impact on quality of life The correlation between anaemia and fatigue has been demonstrated by several studies (Romito et al., 2008). It is proposed that anaemia may be caused of either a consequence of the cancer disease or by the myelo-suppressive chemotherapy due to the elevation of cytokines IL-1, IL-6 and TNF which in turn suppress the production of red blood cells (Kurzrock, 2001). The severity of anaemia varies depending on the degree of the disease and the type of treatment that the cancer patient is undergoing.

2.4.6 Cachexia

Cachexia is among other symptoms also a factor associated with the development of fatigue (Kalman, 1997; Gutstein, 2001). The aetiology of cachexia is multi-factorial and the mechanisms attributable to the development are complex. Among these the accumulation of cytokine by-products occurs due to cellular damage, which interferes with the hypothalamic control of hunger. Loss of appetite caused by cachexia results in a decrease in muscle mass which then leads to weakness and weight loss. Cachexia decreases quality of life and the performance status.

2.4.7 Variation in fatigue and co-existing symptoms over time

A relation exists between rated fatigue and the rated severity of other symptoms following chemotherapy. A study has found that fatigue, insomnia, depression, pain and anxiety were

all positively correlated with one another (Ahlberg et al., 2003). The close link between these symptoms suggests that common mechanisms could underlie their development. There is a high inter- and intra-individual variability in symptom severity including fatigue, a problem well-known from qualitative questionnaires.

3. Fatigue interference with quality of life

Development of fatigue is not only found to be the most frequently reported symptom but it has also a substantial impact on the patients' quality of life in cancer. Impairments in activity, work, concentration, socializing and mood are obvious. Fatigue interferences with the quality of life at the first week after chemotherapy administration followed by a decline the two next weeks (Curt et al., 2000, Diaz et al., 2008). It is noted that the ability to work, the activity level as well as concentration capability are equally affected during the first week.

The patients' perception of their exhaustion and how it interferes with their ability to concentrate and work was reported in a study interviewing patients receiving adjuvant treatment for breast cancer and statements are listed: "*I was probably more mentally worn out, which was why I have not worked so much. But I have still felt ok.* Another patient stated: "*There are some difficult concepts to work with. My situation offers concentrations difficulties, but I have doubts whether it is influenced by the amount of medication*" (Adnan et al., 2010) .

These findings indicate that higher activity and mood as well as the ability to work, socialize and concentrate are increased when fatigue is rated low. This evidence demonstrates that fatigue has a profound impact on quality of life including physical and psychosocial aspects. It also points to the importance of managing fatigue and all other factors contributing to its occurrence. It is observed that a high prevalence of fatigue together with sleep disturbances, anxiety, diarrhoea, depression, constipation and pain, correlates with a decrease in quality of life. Jacobsen et al. (2007) suggested that fatigue is a major problem negatively impacting cancer patients' quality of life. However, it should not be ruled out that the other symptoms besides fatigue may also contribute to the impairment of cancer patients' quality of life.

4. Mechanisms of fatigue

The patho-physiology of fatigue is still not well understood although fatigue symptoms following severe disease particularly cancer and cytotoxic drug treatment have been well-known since long. The molecular mechanisms behind fatigue were although recently proposed by Hartvig-Honoré (2010). A comparison of the symptomatology in permanent and transient disturbances of brain neuromodulation enhances the basic knowledge on regulation factors, e. g. depressive behavioural changes after exhausting exercise or in fatigue. This consideration includes that the interaction between altered central neuromodulation and peripheral metabolic or hormonal dysfunctions is able to initiate the symptoms (Aistars et al., 1987). It is suggested that the central neuromodulation disturbance of stress-induced symptoms initiates the manifestation of the impairment (Hartvig-Honoré, 2010).

The symptoms of fatigue are sometimes divided in those with a peripheral origin and those due to a stress of the brain (Hann et al., 1998). Both types of symptoms might be present

simultaneously. Symptoms from peripheral exhaustion may depend on neuromuscular malfunction or are related to deficiencies in peripheral neurotransmission. These symptoms are often related to immunologic mechanisms induced by the disease as well as its treatment and are accompanied by a release of cytokines (Swain, 2000.) The cytokines may in turn cause "stress" to the brain and change central neurotransmission.

4.1 Peripheral changes of importance for fatigue

One of the theories claims that cancer- and cytotoxic induced fatigue is due to accumulation of various metabolites such as lactate, hydronium ions and cell destruction end products (Piper et al., 1987). Lactate production is increased in cancer. Hydronium ions formed from lactate accumulation may impede muscle force and reduce the number of active actinomycine interactions (Piper et al., 1987).

4.2 Effects of cytokines

Although it has not been definitely proven it is suspected that cytokines such as interleukins, interferon and tumour necrosis factor, TNF- α play a significant role in fatigue, (Blackwell & Christman, 1996). Elevation of the pro-inflammatory cytokines interleukin-1β (1L-1β), IL-6 and tumour necrosis factor TNF-α concentrations is observed in both cancer and its treatment (Blackwell & Christman, 1996; Altar, 1999). Significant correlations with fatigue have been observed for increased interleukin-1 concentrations in men under irradiation therapy for prostate cancer and similarly interleukin elevations were observed in lung cancer patients treated with cytotoxic drugs (Tartaglia & Goeddel, 1992). Cytokines are a category of protein-signaling molecules that are used extensively in cellular communication. The elevation of these cytokines triggers the manifestation of several symptoms such as fever, anaemia, cachexia as well as fatigue (Anisman et al., 1992). These cytokines are produced by macrophages, monocytes and dendrite cells and are also known to be linked to an altered nervous system (Cella et al., 1998; Bower et al., 2007). IL-6 has mainly been considered a pro-inflammatory protein, but there are several lines of evidence that it has anti-inflammatory actions as well (Chao et al., 1991). Of the anti-inflammatory properties of IL-6 function is to modulate pro-inflammatory response, increase C-reactive protein as well to increase cortisol concentrations (Steensberg et al., 2006). TNF-α blockade may reduce fatigue.

It is not known to what extent a peripheral increased interleukin release may affect brain function, but increased penetration over the blood-brain barrier or vagus stimulation are plausible suggested mechanisms. In turn, this may lead to effects on microglia activation and synapse function.

4.3 Changes of central neurotransmission

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

concentrations (Geinitz et al., 2001). In this way fatigue resembles key elements in depression and related disorders.

Cytokines are released in severe disease and during treatment (Kurzrock 2001). Of these, IL-1β, IL-2 and IL-6 have been of particular interest. Interleukins activate the hypothalamus-pituitary axis which controls CRH release (Steensberg et al., 2006), and is closely linked to serotonergic and noradrenergic neurotransmission. A close link between serotonin (5-HT) and TNF-α has been established and TNF-α may change the serotonin metabolism by increasing the neuronal release of 5-HT. Increase of 5-HT transport is seen, which thereby may decrease the concentration of 5-HT in the synaptic space. This feed-back loop between 5-HT and TNF-α might be dysfunctional in the case of increased cytokine release due to treatment. An increase in the functioning of the HPA-axis leads in addition to increased concentrations of cortisol, which in turn is controlled by the interaction of 5-HT with the HPA-axis (Larish et al., 2001; Bower et al., 2002; Morrow et al., 2002). Cytotoxic drugs as well as irradiation therapy impair the cell proliferation and may destroy endogenous microglia cells as well as hippocampus neurons and create an inflammatory response and impaired maintenance and control of the synapses (Bilbo et al., 2009).

4.4 Brain stress and corticotropin hormone release

Central fatigue symptoms are related to alteration in neurotransmitter function in the central nervous system, and accompanied by psychic distress seen as e.g. anxiety and depression (Hann et al., 1998). There are several hypothesis involved to explain the brain stress in fatigue. Stress can be described as non-specific and affecting any demand, activity or emotion and may lead to a state of alarm involving the sympathetic nervous system. Over extended time periods this depletes body reserves and a restoration system is necessary for protection (Aistars, 1987). According to other hypotheses, a system located in the midbrain and medulla of the brain may mediate stimuli that give rise to stress response. Inhibition of the system results in fatigue due either to inhibition of cortical activity due lowered sensory input or as a result of chronic stimulation of the system. (Aistars, 1987).

Stress and depression may decrease cortical input as well, but there are individual factors of great importance to resist the manifestations of the response. CRH in the brain and the HPA axis regulate stress and control the release of adrenocorticosteroid hormone, ACTH,"stress related hormone". CRH containing nerve fibres are projected to the hypothalamus and other brain centres. Studies in rats with a failing CRH release show pronounced alterations in these projections. Long term changes as in chronic disease show a suppression of the ACTH/CRH response both in animal models and in patients (Hann et al., 1998). Deterioration of neurones in the central nervous system e.g . hippocampus has been shown possible to repair by action of neurotrophic factors such as Brain Derived Neurotrophic Factor, BDNF (Hong et al., 1995).

4.5 The role of Brain Derived Neurotrophic factor in stress and exercise

One treatment remedy both in depression and fatigue is simple exercise. Exercise in the form of voluntary running has been shown to increase the concentration of mRNA of the neuron repairing- and neuro-protective substance Brain Derived Neurotrophic Factor, in the hippocampus, cerebral cortex and other areas of the brain (Mamounas et al., 2000; Swain et

al., 2000). In contrast, acute stress decreases BDNF mRNA in the hippocampus (Adlard et al., 2004). BDNF may have a protective role in acute stress. Following immobilization, circulating corticosteroid concentrations were elevated and showed a reduction of the BDNF protein (Adlard et al., 2004). Rats given voluntarily access to running prior to the stress demonstrated significantly increased hippocampus BDNF as well as corticosteroid concentrations that remained high (Adlard et al., 2004). In animals without exercise the BDNF concentrations decreased shortly after stress. Thus, corticosteroids modulated the stress-related changes of the BDNF protein (Adlard & Cotman, 2004).

Exercise may override the negative effects of stress with remaining high concentrations of both corticosteroids and BDNF. Voluntary physical activity may, according to clinical observations and the study on treatment of cancer and cytotoxic induced fatigue (Adamsen et al., 2006; Andersen et al., 2006; Midtgaard et al., 2009) represent a simple non-pharmacological tool for maintenance of the neutrophin, e.g. BDNF concentrations in the brain. This hypothesis needs clinical validation, however.

There is a link to effect of exercise to serotonin regulation in the brain. Simple exercise has been a remedy for both cancer- and cytotoxic related fatigue and may give an exercise-induced increase of free tryptophan in blood due to liberation from albumin, which is caused by adrenergic induced lipolysis of free fatty acids and results in higher free tryptophan uptake into the brain. Consecutively enhanced serotonin biosynthesis may though not per se initiate mood improvement or battle central fatigue. In this context the neurodegenerative effect of kyuneric acid a metabolite of tryptophan has been implied as a further contribution to brain alteration playing a role in fatigue. Centrally originated fatigue, mental deficiency and behavioural alterations with depressive mood are probably not primarily caused by metabolic and neuromuscular alterations. The primary trigger of these transient behavioural alterations might instead be initiated by a central exhausting stress, which elicits impairment of complex neuromodulation, also afflicting the interaction of central neurotransmitters or hypothalamic neuropeptides as well as releasing factors. In a consecutive correction of the variation, the implication of the serotonergic system on the central neuromodulation disturbance might improve or prevent the progressive course both in transient and in permanent mental disorders. Similar mechanisms of a central stress might be implicated in fatigue, and might be battled by simple exercise due to a peripheral exhaustion (Adamsen et al., 2006; Andersen et al., 2006; Midtgaard et al., 2009).

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 (Redeker et al., 2000, Hartvig Honoré, 2010)), and the exact mechanisms are not completely known. The contribution of each factor may vary between patients and in individual patients over the courses of illness and treatment. The degree of fatigue might also differ between diseases and cancer types (Hartvig et al., 2006a; Hartvig et al., 2006b).

5. Physical activity and fatigue

Physical exercise is often an intervention proposed in order to reduce fatigue. This evidence is congruent with the majority of studies investigating the relation between fatigue and physical activity (Midtgaard et al., 2009). A correlation between the number of days during which the patients have been active per week and fatigue prevalence was shown. It is

noticed when number of physically active days increases it correlates with decreasing intensity of worst fatigue. Thus, it is noticed that fatigue is a major hindrance to physical activity (Schwartz, 2000).

Several studies support the benefits of physical exercise to manage fatigue during and after treatment. Breast cancer patients exercising on a regular basis showed a decrease in fatigue (Schwartz, 2000; Andersen et al.,2006). The apportioned outcomes of physical exercise during chemotherapy treatment resulted in decreased fatigue and hence improved quality of life. Voluntary exercise in rats has recently shown the same effect on BDNF (Adlard et al., 2004).

One of the essentials of managing fatigue is to give patients adequate information about physical exercise. This was surveyed by Hartvig et al (2006b) showing a significant decrease in fatigue severity after education information as compared to patients not provided with adequate information regarding physical activity. Not sufficient information was considered to be a hampering aspect in fatigue management. (Adamsen et al., 2006). It is important to carefully consider which type of exercise that may be most beneficial. The kind of physical activity is usually not investigated in surveys. Moderate intensity and tailored physical activities for each patient reduces fatigue significantly in cancer patients undergoing treatment (Adamsen et al., 2006).

6. Treatment targets for fatigue related syndromes

Modulation of interleukin release and control of different neurotransmitter systems in the brain as well as promotion of BDNF synthesis and release are new options to challenge fatigue. There are thus several targets for treatment of fatigue syndromes apart from the non-pharmacologic simple exercise. Since fatigue is accompanied by several other distressing symptoms, the recommended best treatment for fatigue is to treat all underlying symptoms such as insomnia, pain, diarrhoea, constipation, anaemia etc (Kalman, 1997). In particular anaemic patients, supplementation with erythropoietin and similars has been successful, but the intervention is more to support an underlying symptom of the fatigue (Demetri et al., 1998; Kim et al., 2008, Glasby et., 1997), although hippocampus neuron stimulation may be included among the effects. A further remedy is corticosteroids but they can only be used for a limited time.

6.1 Pharmacologic interventions

Pharmacological treatment has so far had limited success, but new principles should be further developed. The serotonin system is a target and contributor to the neurobiology of stress (Nitta et al., 1994). There are implications that the stimulation of the serotonin 5-HT_{2A} receptor mediates the increase (Rosel et al., 2000; Rumajogee et al., 2002), but also the decrease of corticosteroids (Sapolsky et al., 1990). Elevated concentrations of glucocorticoids are known to play a notable role in the stress-induced damage of the brain (Shirayama et al., 2002). Corticoids and acute or long-term stress are shown to depress the expression of the serotonin transporter and BDNF (van Loon et al., 1981., Stockmeier; 2003). There are indications that the stress-derived decrease of BDNF is mediated by the serotonin 5-HT_{2A} receptor. The down regulation of BDNF may contribute to the atrophy of neurons in response to stress. Several antidepressant treatments increase the mRNA concentrations of BDNF (Watanabe et al., 2003).

6.1.1 Brain derived neurotrophic factor

Infusion of BDNF itself in the brain creates antidepressant-like effects, and increases the concentration of serotonin transporter, serotonin and its metabolites. BDNF may in fact attenuate corticoid-induced neural cell death by producing regenerative sprouting of injured serotonergic nerve terminals (Adlard et al., 2004). In order to understand the stress induced fatigue and the depressant state, it is essential to reveal the mechanisms of which BDNF and corticoids regulate serotonin and 5-HT_{2A} receptor concentrations which may form new interesting targets to combat fatigue. There is information on the regulation of BDNF expression by different antidepressants or serotonin receptor agonists and antagonists (Piper et al., 1987), but there is a substantial gap in the knowledge of the regulatory effects of BDNF on the receptor level. In conclusion, a working hypothesis is that BDNF regulates the expression of 5-HT_{2A} serotonin receptors, and that corticoids may act negatively upon this action (Piper et al., 1987).

6.1.2 Serotonergic drugs

Treatment of fatigue with other serotonin modulating drugs has been tried such as serotonin re-uptake inhibitors and other antidepressant drugs but the effect was not satisfactory. Fatigue symptoms have also been managed by treatment with 5-HT serotonin receptor agonists. It is obvious that more selective tools for interaction in specific processes in serotonin turn-over and binding should be further explored. Psycho-stimulants enhancing serotonin concentrations have a short but limited time effect and the risks of tolerance, dependence and other side effects can not be overlooked

6.1.3 Cytokines

Cytokine treatment causes fatigue. Intervention in the interleukin balance might be another target for treatment. It is obvious that IL-6 also has anti-inflammatory actions thereby causing a feed back effect (Steensberg et al., 2006). In fact the time course of IL-6 closely corresponds to the timing of fatigue after cytotoxic drug treatment (Tartaglia & Goeddel, 1992) and may therefore have a positive effect on fatigue.

6.1.4 Future perspectives for treatment

Recently the causes and consequences of fatigue have been more focused seemingly because it is a devastating state and most suffering in many diseases. The interest has been pointed both to peripheral and to central mechanisms to explain fatigue. It is likely that different mechanisms may interact and aggravate the problem, meaning that multimodal treatments must be tried. Normal sleep seems to be a mainstay as in other depressive and exhaustion disorders. Patients with fatigue often experience a disrupted sleep and an early awakening. So far exercise is the most promising algorithm which seems contradictory in a state with severe exhaustion and tiredness. The pedagogic message to the patient should be that by exercise they may get a muscle tiredness that may successfully combat the brain excitation due to the fatigue stress and may cause tiredness to the brain. Simultaneously, other signs that aggravate fatigue must be treated (Kalman, 1997). At present a curing pharmacological treatment for fatigue seems not possible.

7. Conclusions

Fatigue is a significant clinical problem during chemotherapy in cancer. As a confirmation to this, 100% of breast cancer patients have reported to experience fatigue immediately after the start of chemotherapy treatment. Cancer patients even report fatigue at baseline followed by a statistically significant increase in fatigue severity after treatment initiation. The chemotherapy induced fatigue is transient as the fatigue declines at the end of treatment cycle as the patients are slowly recovering.

Chemotherapy induced fatigue is found to be a more predominant symptom occurring as compared to others like sleep disturbance, being more prevalent than unrest > anxiety > diarrhea > depression > constipation and pain. A close time relation between the different symptoms and fatigue may be observed throughout the treatment. This evidence points to the complexity of managing fatigue due to its co-relation with other symptoms. Further risks for fatigue are young age, female gender and type, length and severity and type of tumor disease as well as type of chemotherapy drugs used and concomitant radiotherapy. Fatigue had a major impact on patient's quality of life on the daily basis comprising both physical and psychological aspects. All these findings confirm the multi-dimensional nature of fatigue and emphasize the importance of a multimodal treatment approach. Successful treatment algorithms are not many so far. Apart from careful management of all co-existing symptoms, only a moderate daily exercise has found some impact on the symptom with earlier vanish of fatigue but also less disturbing symptoms.

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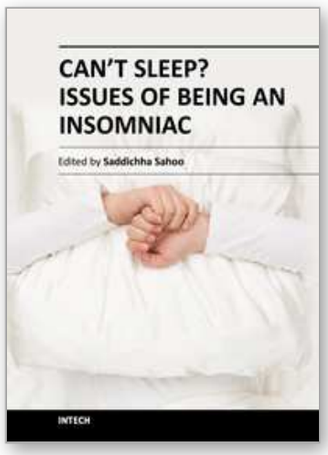

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The word insomnia originates from the Latin "in" (no) and "somnus" (sleep). It is a disorder characterized by an inability to sleep or a complete lack of sleep. Various studies have noted insomnia to be quite a common condition, with symptoms present in about 33-50% of the adult population. This book provides a comprehensive state of the art review on the diagnosis and management of the current knowledge of insomnia and is divided into several sections, each detailing different issues related to this problem, including epidemiology, diagnosis, management, quality of life and psychopharmacology. In order to present a balanced medical view, this book was edited by a clinical psychiatrist.

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