

Is it Tiring to Deal with Fatigue?

Omer Gendelman MD and Howard Amital MD MHA

Department of Medicine B, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: fatigue, chronic fatigue syndrome, inflammation, fibromyalgia, cancer

IMAJ 2012; 14: 566-567

Fatigue is a common yet underestimated and undervalued symptom of many medical conditions, and is often one of the initial complaints that leads a patient with a developing chronic illnesses to seek medical care [1,2]. Fatigue should be distinguished from somnolence, dyspnea and muscle weakness, although these symptoms may often coexist. By definition it is different from the normal recognized experience of tiredness or sleepiness. Therefore, this symptom is by nature non-specific and highly subjective. Clinical fatigue incorporates three main components that present varyingly in individuals: inability to initiate activity (perception of generalized weakness in the absence of objective findings), reduced capacity to maintain activity (easy fatigability), a subjective feeling of cognitive deficit such as difficulty concentrating and a sensation of memory deficit often with concomitant emotional instability (mental fatigue) [3,4].

Fatigue is often the major problem and concern of patients with various medical conditions. Cancer-related fatigue is profoundly related to physical, psychosocial and occupational aspects. Fatigue is routinely identified by patients as one of the most distressing symptoms associated with cancer and its subsequent treatment. It is often underreported and overlooked by many health care providers, or regarded erroneously as potentially

remediable by treating the primary underlying condition [1]. The prevalence of cancer-related fatigue varies widely, ranging between 50% and 90% of cancer patients, reflecting the diversity of populations as well as the subjective nature of the screening tools used [1].

Fatigue is a common and disabling symptom that has been studied thoroughly in many inflammatory conditions such as multiple sclerosis, systemic lupus erythematosus, Sjogren's syndrome, chronic liver disease, rheumatoid arthritis and ankylosing spondylitis [2,5-8]. It is an important cause of decreased quality of life among patients with inflammatory arthritis, especially RA [9]. RA patients highlight fatigue as a major concern, as troublesome as pain, often unmanageable and unfortunately often ignored by clinicians [10]. Significant fatigue occurs in up to 70% of patients with RA and is more complex to cope with [11]. Since underlining fatigue is addressed in many RA patients, there has been an international investigational consensus that it be measured and included in all RA clinical trials.

Fatigue is multidimensional; in RA patients it is highly correlated with disease activity but bears no linkage to the classical inflammatory parameters such as erythrocyte sedimentation rate or concentrations of C-reactive protein, or to the swollen or tender joint counts [12]. On the other hand, Cutolo et al. [13,14] described the temporal relationship between elevated levels of pro-inflammatory cytokines and symptoms of RA, such as morning stiffness, nocturnal pain, and fatigue. Interestingly,

interferon-gamma, interleukins-1, 6, 2 and 12, and tumor necrosis factor-alpha production (pro-inflammatory cytokines) reach their peak during the night and early morning, shortly after melatonin serum levels are at their highest and plasma cortisol at their lowest. In inflammatory conditions melatonin concentrations plateau for 2-3 hours, a finding that is not observed in healthy controls, possibly leading to excessive inflammatory cytokine production.

Fatigue is a well-recognized and significant component of the fibromyalgia syndrome and of the chronic fatigue syndrome. Fatigue is one of the primary parameters of the new set of classification criteria of the fibromyalgia syndrome [15]. In these patients, the activity of the central nervous system descending anti-nociceptive pathways is decreased, as evidenced by lower cerebrospinal fluid levels of serotonin, norepinephrine and dopamine metabolites. Similar imbalances of these neurotransmitters in different brain regions interfere with the normal neuroprocessing mechanisms, resulting in the characteristic impaired mood, energy and sleep, and increased fatigue [16].

Fatigue is also often encountered in primary care. A recent study noted that complaints of fatigue affected as much as one-third of the general population, with 5% short-term fatigue (< 6 months), 31% chronic fatigue (> 6 months), and 1% chronic fatigue syndrome-like fatigue [17]. It concurs with pain and is often augmented by other factors such as sleep problems, distress, anxiety or depression, negative life events, use of psychoactive medications and others. Van't Leven and colleagues [17] reported that fatigued subjects are often charac-

RA = rheumatoid arthritis

terized as having unhealthy life habits such as smoking, unhealthy food, insufficient physical activity, and excessive use of analgesics, antidepressants and sedatives. Other prospective population-based studies found that previous psychiatric disorders, stress and emotional lability are important predictors for the development of chronic fatigue [18,19].

In this issue of *IMAJ* Kitai et al. [20] retrospectively investigated the clinical characteristics of almost 300 patients who visited their general practitioner due to unexplained fatigue (after excluding those individuals who had a coexisting chronic disease). Similar to other ill-defined medical conditions, women comprised almost 70% of the population. The most common accompanying complaints were dizziness, headaches and insomnia. Not surprisingly the yield of the multiple tests that were done was extremely low and probably far from being cost effective. The authors state that even among those patients in whom mild anemia was detected, therapy did not resolve the subjective feeling of fatigue.

These interesting results corroborate previous observations that fatigue in general and acute fatigue in particular belong to the wide category of ill-defined medical conditions such as chronic fatigue syndrome, fibromyalgia, migraines, irritable bowel syndrome and others. Modern life and modern medicine challenge us medical professionals to identify these individuals and to treat them with attention and thoughtfulness and not by avoidance or cynicism as we often unfortunately

do. This attitude is also economically justified given the high costs of medical investigations, mostly futile, that these patients are often put through.

We believe that general practitioners have a significant advantage owing to their continuous acquaintance with their community. This ongoing familiarity with the individual patient empowers them to adopt a rather “holistic” approach, referring these patients to secured and less busy “time zones” in their schedule, which is far more effective and undoubtedly less medically defensive and costly. Such an action will probably prevent these patients from undergoing unnecessary and sometimes harmful medical procedures.

Corresponding author:

Dr. H. Amital
 Head, Dept. of Medicine B, Sheba Medical Center,
 Tel Hashomer 52621, Israel
Phone: (972-3) 530-2661
Fax: (972-9) 530-4796
email: hamital@netvision.net.il, howard.amital@sheba.health.gov.il

References

1. De WS, Van BS. Cancer-related fatigue. *Acta Clin Belg* 2010; 65: 378-85.
2. Swain MG. Fatigue in liver disease: pathophysiology and clinical management. *Can J Gastroenterol* 2006; 20: 181-8.
3. Barsevick AM, Cleeland CS, Manning DC, et al. ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage* 2010; 39: 1086-99.
4. Cathebas PJ, Robbins JM, Kirmayer LJ, Hayton BC. Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. *J Gen Intern Med* 1992; 7: 276-86.
5. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* 1984; 65: 135-8.
6. Jones SD, Koh WH, Steiner A, Garrett SL, Calin A. Fatigue in ankylosing spondylitis: its prevalence and relationship to disease activity, sleep, and

other factors. *J Rheumatol* 1996; 23: 487-90.

7. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. *Expert Rev Neurother* 2010; 10: 1437-47.
8. Swain MG. Fatigue in chronic disease. *Clin Sci (Lond)* 2000; 99: 1-8.
9. Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis Rheum* 2004; 51: 578-85.
10. Minnock P, Bresnihan B. Fatigue is related to poor pain outcomes in women with established rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 707-8.
11. Hewlett S, Cockshott Z, Byron M, et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum* 2005; 53: 697-702.
12. Bergman MJ, Shahouri SH, Shaver TS, et al. Is fatigue an inflammatory variable in rheumatoid arthritis (RA)? Analyses of fatigue in RA, osteoarthritis, and fibromyalgia. *J Rheumatol* 2009; 36: 2788-94.
13. Cutolo M, Maestroni GJ. The melatonin-cytokine connection in rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 1109-11.
14. Cutolo M, Straub RH, Buttgerit F. Circadian rhythms of nocturnal hormones in rheumatoid arthritis: translation from bench to bedside. *Ann Rheum Dis* 2008; 67: 905-8.
15. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 2010; 62: 600-10.
16. Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. *Mayo Clin Proc* 2011; 86: 907-11.
17. Van't Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health* 2010; 20: 251-7.
18. Harvey SB, Wadsworth M, Wessely S, Hotopf M. The relationship between prior psychiatric disorder and chronic fatigue: evidence from a national birth cohort study. *Psychol Med* 2008; 38: 933-40.
19. Kato K, Sullivan PF, Evengard B, Pedersen NL. Premorbid predictors of chronic fatigue. *Arch Gen Psychiatry* 2006; 63: 1267-72.
20. Kitai E, Blumberg G, Levy D, Golan-Cohen A, Vinker S. Fatigue as a first-time presenting symptom: management by family doctors and one year follow-up. *IMAJ Isr Med Assoc J* 2012; 14: 555-9.

There is no conversation more boring than the one where everybody agrees

Michel de Montaigne (1533-1592), French essayist

I have taken more good from alcohol than alcohol has taken from me

Winston Churchill (1874-1965), British Conservative politician and statesman known for his leadership of Britain during the Second World War, and twice Prime Minister. A noted statesman and orator, Churchill was also an officer in the British Army, historian, writer and Nobel Prize laureate (Literature)