

Normal and abnormal fatigue

Fatigue is normal after a high level of physical exertion and forces us to take the rest that is necessary for our muscles to recover. Fatigue is the inability to maintain a specific level of normal physical activity or lack of endurance. Endurance is determined by the ability of the cardiovascular system to supply the muscles with oxygen and remove the products of metabolism.

Abnormal fatigue may be defined as a lack of endurance when we undertake a normal physical activity. However, fatigue has many more aspects and is more complex as a medical problem. It can be characterized in terms of intensity, duration, and effects upon daily function. In population-based studies, 20% of healthy adults reported persistent fatigue. Among patients with autoimmune disease, the prevalence of fatigue is in the range of 60–70%.

Weakness can be confused with fatigue, particularly since they are sometimes both present at the same time. Weakness is a reduction of normal power. If, when walking upstairs, a person is unable to go further than the first step, this is probably weakness. However, if this only occurs on the tenth step, it may be a question of fatigue.

Causes of fatigue

There are many causes of abnormal fatigue (table 6.1).

Cardiovascular disorders are a very common cause

Table 6.1 Several general causes of fatigue

- heart failure
- anaemia
- depression
- metabolic disorders
- deficiency of vitamin D
- hormonal disorders
- autonomic neuropathy (low blood pressure)
- psychiatric disorders
- autoimmune disorders
- infectious diseases
- malignancies
- drugs

due to insufficient blood supply to the tissues.

Depression can also be a cause of fatigue. In the case of depression, a patient may already feel tired on getting up in the morning and there is no association with exertion (so no lack of endurance).

FATIGUE AND SJÖGREN'S SYNDROME

In Sjögren's syndrome, fatigue can have a number of different causes (see table 6.2). It is important to do everything possible to discover what the cause is, since the possibility of treating the fatigue may be directly related to this. It is unfortunately by no means always possible to discover the cause. Some causes of fatigue, such as anaemia, may in turn have a number of possible origins. Most of the disorders listed in table 6.2 speak for themselves or have already been discussed.

Distal renal tubular acidosis (DRTA) occurs in 50% of Sjögren's syndrome patients, usually in a mild form. DRTA is discussed in chapter 2. DRTA causes metabolic acidosis and compensatory hyperventilation

Table 6.2. Several causes of fatigue in Sjögren's syndrome

- inflammation of muscles and joints
- anaemia
 - chronic inflammation
 - iron deficiency
 - blood loss in stomach or intestines (e.g. caused by medication such as NSAIDs)
 - inflammation
 - vitamin B12 deficiency
 - haemolysis
- sleep disturbances
- depression
- distal renal tubular acidosis (DRTA)
 - hyperventilation
 - hypokalemia (muscle weakness)
- thyroid disorders
- hyperviscosity
- hypotension (low blood pressure, e.g. due to autonomic neuropathy)
- deficiency of vitamin D

... loss of physical functioning is independent of general fatigue, mental well-being, and depressive mood.

*Hartkamp et al (2008)*⁶

to correct the acidosis. More pronounced DRTA causes hypokalemia (low serum potassium). Moderate hypokalemia may cause muscular weakness, myalgia, and muscle cramps, and constipation (disturbed function of skeletal and smooth muscles, respectively). With more severe hypokalemia, flaccid paralysis, hyporeflexia, and tetany may result. Severe fatigue may be caused by the compensatory chronic hyperventilation.

Hypotension (low blood pressure) may result from autonomic neuropathy (see chapter 8) and has been found to be correlated with fatigue in Sjögren's patients.¹

In SLE patients, vitamin D deficiency has been found to correlate with fatigue while hydroxychloroquine treatment prevented vitamin D deficiency.²

Fatigue without a known cause

In many patients with Sjögren's syndrome no specific cause of fatigue can be found.

Barendregt *et al* assessed fatigue in relation to depression, blood pressure, and plasma catecholamines in patients with primary Sjögren's syndrome (pSS), in comparison with healthy subjects (HS) and patients with rheumatoid arthritis (RA).³ For the assessment of fatigue the so-called Multidimensional Fatigue Inventory (MFI) was used, a 20 item questionnaire, covering the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.¹⁰ Each dimension is represented by four items, two of which indicate fatigue and two of which are contradictory of fatigue (see box). Patients with pSS were found to be more fatigued compared with HS on all the five dimensions of the MFI. In the pSS patients, significant positive correlations between depression and the dimensions of reduced motivation and mental fatigue were found. Comparing patients with pSS with those with RA, using depression as covariate, no statistically significant differences were found between these groups.

Bax *et al* found that fatigue differed significantly from that of HS and that fatigue was equally raised in patients with primary and secondary Sjögren's syndrome.⁴ Further analysis showed that 79% of the fatigue in patients with pSS could be explained by depression, total level of immunoglobulins, and thrombocyte counts ($p < 0.001$). Both depression and thrombocyte counts showed a significant positive

correlation, whereas levels of immunoglobulins showed a negative correlation. Increased numbers of thrombocytes is an inflammatory acute phase reaction. Despite that no significant correlation between thrombocyte counts and CRP levels were found, the finding suggests that low-grade inflammation may cause or worsen fatigue.

Godaert *et al* examined various aspects of fatigue in the daily life of female patients with pSS and SLE and in HS.⁵ They compared age-adjusted, repeated measurements of fatigue across the day. General and physical fatigue was significantly higher in patients than in HS. Groups did not differ with respect to average levels of reduced motivation or mental fatigue. Both general and physical fatigue and reduced activity varied significantly during the day. Adjusting for depressive symptoms, groups showed significantly different time courses during the day. In HS and patients with SLE, fatigue first decreased and then

Multidimensional Fatigue Inventory¹⁰

The Multidimensional Fatigue Inventory (MFI) consists of 20 items grouped in five dimensions (facets). The responder indicates on a 1-to 5-point scale to what extent the statement applies to him or her.

general fatigue

- fit
- tired
- rested
- tire easily

physical fatigue

- do little
- take on a lot
- physically bad condition
- physically excellent condition

reduced activity

- very active
- do a lot in a day
- do very little in a day
- get little done

reduced motivation

- want to do nice things
- dread doing things
- lots of plans
- don't feel like doing anything

mental fatigue

- keep my thoughts
- concentrate well
- effort to concentrate
- thoughts easily wander

Table 6.3 PROFAD-SSI: fatigue and discomfort questionnaire (Bowman *et al* ⁷)

1. feeling a need to rest	11. a lack of strength in my muscles
2. tiredness	12. feeling weak
3. feeling exhausted	13. not thinking clearly
4. wanting to lie down, to sleep	14. it's hard to concentrate
5. it's hard to GET going	15. forgetting things
6. things taking an effort	16. making mistakes
7. feeling "it's a battle"	17. discomfort
8. it's hard to KEEP going	18. pain
9. feeling easily worn out	19. aching all over
10. a lack of energy	

The 16-item ProF consists of questions on items 1 to 16.⁹

increased, whereas a rather opposite course - at least for the first part of the day - was observed in patients with pSS. Using an ecologically valid assessment method, they demonstrated substantially higher levels of daily fatigue in SLE and pSS patients as compared to HS, thereby jeopardizing these patients' quality of life. Hartkamp *et al* studied the effect of dehydroepiandrosterone (DHEA) on fatigue, well-being, and functioning in women with pSS in a double-blind, randomised placebo-controlled clinical trial.⁶ Patients from both the DHEA and placebo-treated group improved on general fatigue, mental well-being, and depressive mood but physical functioning did not change. This indicates that loss of physical functioning is independent of general fatigue, mental well-being, and depressive mood.

Bowman *et al* developed a measure of fatigue and general discomfort from words in which patients with

SF-36®

The Short Form (36) Health Survey® is a survey method of patient health. The SF-36® consists of eight scaled scores, which are the sums of the questions in their section. Each scale is transformed into a 1-100 scale on the assumption that each question carries equal weight.

The eight sections are:

- vitality
- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning
- mental health

See table 6.4 for further details.

Fatigue, depression and fibromyalgia

The results of this study did not support the hypothesis that the fatigue associated with Sjögren's syndrome can largely be accounted for by increased levels of depression or fibromyalgia.

Bowman et al (2004) ⁷

pSS expressed their complaints of fatigue, discomfort and pain.⁷ It is referred to as the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI). The questionnaire asks patients to rate the worst problems they experienced over the last two weeks with a number between 0 (not present at all) and 7 (as bad as imaginable). The 19 symptoms are listed in table 6.3.

The PROFAD-SSI was compared with other scores such as the Medical Outcome Study Short-Form 36 (SF-36®, see window and table 6.4), the brief form of the World Health Organization's Multicultural Quality of Life Instrument (WHOQOL-BRF) and the Hospital Anxiety and Depression Scale (HAD) scales.

Psychosomatics, gastric ulcers and Helicobacter pylori

In general, the medical world tries to explain as much diseases, disorders and complaints as possible. As long as the explanations are based on facts it's ok. But sometimes explanations are presented for which no scientific evidence exists at all.

Very popular are explanations that are based on the way our brains work and may cause organic disease. The scientific evidence usually lacks or is very controversial. Moreover, psychosomatic explanations are often regarded as it is between your ears, it is all in your mind or even it is your own fault.

A clear example is the story of a gastric ulcer that was considered to be a psychosomatic disease in the sixties and seventies.⁸ It was ascribed to severe psychopathology.

Today we know that the bacterium *Helicobacter pylori* plays a crucial role in causing gastric ulcers. Moreover, eradication of this bacterium usually heals the ulcers.

The lesson to be learnt is that the medical and lay world better replaces the term "psychosomatic" by "unexplained" as long as a real psychosomatic cause of a disease has not been demonstrated.

Table 6.4 Rand Health scores for quality of life SF-36®

All of the surveys from RAND Health such as the SF-36, SF-20 and SF-12 are public documents, available without charge (for non-commercial purposes).

Instructions

Scoring the SF-36 is a two-step process. First, precoded numerical values are recoded. All items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are set at 0 and 100, respectively. In step 2, items in the same scale are averaged together to create the 8-scale scores (see the RAND website for detailed instructions). See: http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html

RAND 36-Item Health Survey 1.0 Questionnaire Items

1. In general, would you say your health is: Excellent 1 Very good 2 Good 3 Fair 4 Poor 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle One Number on Each Line)

	<u>Yes, limited a lot</u>	<u>Yes, limited a little</u>	<u>No, not limited at all</u>
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle One Number on Each Line)

	<u>Yes</u>	<u>No</u>
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	<u>Yes</u>	<u>No</u>
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

(Circle One Number)

Not at all 1 Slightly 2 Moderately 3 Quite a bit 4 Extremely 5

21. **How much bodily pain have you had during the past 4 weeks?**

(Circle One Number)

None 1 Very mild 2 Mild 3 Moderate 4 Severe 5 Very severe 6

22. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

(Circle One Number)

Not at all 1 A little bit 2 Moderately 3 Quite a bit 4 Extremely 5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .

(Circle One Number on Each Line)

	<u>All ..</u>	<u>Most ..</u>	<u>A Good Bit ..</u>	<u>Some ..</u>	<u>A Little ..</u>	<u>None ..</u>
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

(Circle One Number)

All of the time 1 Most of the time 2 Some of the time 3 A little of the time 4 None of the time 5

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

	<u>Definitely True</u>	<u>Mostly True</u>	<u>Don't Know</u>	<u>Mostly False</u>	<u>Definitely False</u>
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Table 6.5 The Fatigue Severity Scale Questionnaire.¹²

1. My motivation is lower when I am fatigued
2. Exercise brings on my fatigue
3. I am easily fatigued
4. Fatigue interferes with my physical functioning
5. Fatigue causes frequent problems for me
6. My fatigue prevents sustained physical functioning
7. Fatigue interferes with carrying out certain duties and responsibilities
8. Fatigue is among my three most disabling symptoms
9. Fatigue interferes with my work, family, or social life

The subject is asked to circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week (1: not appropriate; 7: agreement). The scoring is done by calculating the average response to the question.

In this study, eight facets of somatic and mental fatigue and general discomfort were compared. For somatic fatigue four facets were used: “need rest”, “poor starting”, “low stamina” and “weak muscles”. Mental fatigue consisted of “poor concentration” and “poor memory”. General discomfort was divided into “discomfort/pains” and “all-over-ache”.

Patients with SLE and RA also completed the questionnaires. Similar patterns of responses were found between patients with pSS and SLE. The authors conclude that the PROFAD-SSI is more sensitive than the other scales to distinguish the three rheumatic disorders from controls. The results of this study did not support the hypothesis that the fatigue associated with Sjögren’s syndrome can largely be accounted for by increased levels of depression or fibromyalgia.

To further test the validity of the PROFAD-SSI, the 16-item profile of fatigue (ProF) containing the first 16 items of the PROFAD-SSI (table 6.3) was compared with the 20-item Multidimensional Fatigue Inventory (MFI).⁹ In this study, it is concluded that both the ProF and the MFI distinguish between somatic and mental fatigue in Sjögren’s syndrome and RA but that the ProF appeared better in resolving somatic facets of fatigue.

Segal *et al*¹¹ investigated the relationship of fatigue to other clinical features in pSS syndrome to identify factors contributing to the physical and mental aspects of fatigue. Fatigue was assessed with a visual analogue scale, the Fatigue Severity Scale (FSS)¹² (see table 6.5) and the ProF. Abnormal fatigue, defined as a FSS score 4, was present in 67% of the subjects.

Fatigue

Fatigue as a cause of full or partial incapacity for work is objectified if Sjögren’s syndrome has been diagnosed.

Pain, helplessness, and depression were the strongest predictors of fatigue. Depression was associated with higher levels of fatigue; however, the majority of subjects with abnormal fatigue were not depressed. Anti-SSA/Ro positive subjects were no more likely to report fatigue than seronegative subjects. The authors conclude that psychosocial variables are determinants of fatigue, but only partially account for it. Although fatigue is associated with depression, depression is not the primary cause of fatigue Sjögren’s syndrome. Segal *et al* further suppose that patients who see themselves as unable to influence or control their condition are more susceptible to fatigue and depression. However, the relationship between helplessness and fatigue remained significant after taking into account the role of depression.

Meijer *et al*¹⁵ also showed that Sjögren’s syndrome has a large impact on health-related quality of life, employment and disability as reflected by lower SF-36 scores and employment rates, and higher disability rates when compared with the general Dutch population. Furthermore, the importance of fatigue in Sjögren’s syndrome was underscored by the fact that the majority of Sjögren’s patients felt tired and 40% ranked fatigue as their most severe symptom. The authors conclude that fatigue should therefore be considered as an important treatment target.

From these studies it may be concluded that fatigue is one of the most severe consequences of Sjögren’s syndrome with a large impact on health-related quality of life, employment and disability. Fatigue is not caused by depression.

The therapeutic approach of fatigue is discussed in chapter 5.

Fatigue and incapacity for work

Patients with Sjögren's syndrome are sometimes unable to (fully) work due to severe fatigue. The question then arises as to whether they are unfit for work. One of the tasks of medical examination authorities is to objectify symptoms that lead to partial or full incapacity for work, principally with the aim of preventing abuse of social benefits. In general terms, a symptom is objectified if an illness has been diagnosed of which the symptom in question is a consequence. Fatigue as a cause of full or partial incapacity for work is therefore objectified if Sjögren's syndrome has been diagnosed.

Conclusions regarding fatigue

- in Sjögren's syndrome fatigue is a very common complaint with sometimes major consequences
- it should always be endeavoured to find a cause
- even if no cause is found, this does not necessarily mean that treatment has no chance of success (see chapter 5)
- adaptation of lifestyle may improve fatigue (see chapter 5)
- fatigue can cause incapacity for work
- fatigue is associated with depression but depression is not the primary cause of fatigue Sjögren's syndrome

CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. CFS is shrouded in mystery. A confusing and incorrect name used to describe this condition is myalgic encephalomyelitis (ME). Some patients with Sjögren's syndrome will have received this diagnosis in the past. As soon as the diagnosis of Sjögren's syndrome has been made, CFS is no longer valid as a diagnosis. The reason for this is that the definition of CFS requires a patient to have no diagnosed diseases that are known to cause fatigue and Sjögren's syndrome is a known cause of fatigue. In other words, CFS is a form of fatigue without a known cause.

Fatigue in CFS differs from fatigue in known diseases because it is not caused by exertion and does not improve by rest.

CFS and human gammaretrovirus

The recent discovery of a gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in the tumor tissue of a subset of USA prostate cancer

patients has prompted Lombardi *et al*¹³ to test whether XMRV might be associated with CFS in the USA. Both XMRV-positive prostate cancer and CFS, have been linked to alterations in the antiviral enzyme RNase L. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, they identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus in 67% of CFS and in 3.7% of healthy controls. Cell culture experiments revealed that patient-derived XMRV was infectious and that both cell-associated and cell-free transmission of the virus were possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. Additional tests suggested that CFS patients mounted a specific antibody response to XMRV that was absent in healthy subjects.

Erlwein *et al*¹⁴ screened 186 CFS sufferers in the UK for XMRV provirus and for the closely related murine leukaemia virus (MLV). While the beta-globin gene was amplified in all 186 samples, neither XMRV nor MLV sequences were detected. Erlwein *et al* conclude that the discrepancy with studies from the USA may be the result of population differences between North America and Europe regarding the general prevalence of XMRV infection. This could also explain the fact that two USA groups found XMRV in prostate cancer tissue, while two European studies did not.

These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS but more studies are clearly needed.

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