

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.

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 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).

Sjögren's syndrome and fatigue

In Sjögren's syndrome, fatigue can have a number of different causes (see table 6.2). It is important to do

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

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 to correct the acidosis.

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

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

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)
- inflammation
- vitamin B12 deficiency
- haemolysis
- sleep disturbances
- depression
- distal renal tubular acidosis (DRTA)
- hyperventilation
- thyroid disorders
- hyperviscosity
- hypotension (low blood pressure) e.g. due to autonomic neuropathy
- deficiency of vitamin D (e.g. due to avoidance of sun)

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

Hartkamp et al (2008) ⁶

(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 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

Multidimensional Fatigue Inventory ¹⁰

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

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 pSS expressed their complaints of fatigue, discomfort and pain.⁷ It is referred to as the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PRO-FAD-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*)

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

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

and 7 (*as bad as imaginable*). The 19 symptoms are listed in table 6.3.

The PROFAD-SSI was compared with other fatigue scores such as the Medical Outcome Study Short-Form 36 (SF-36®), 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.

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

SF-36®

The Short Form (36) Health Survey® is a copyrighted 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

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

questionnaires. Similar patterns of responses were found between patients with Sjögren's syndrome 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.

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. Psychosomatic explanations are often translated in medical practice 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 gastric ulcers that were ascribed to severe psychopathology in the sixties and seventies.⁸

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 world better replaces the term "psychosomatic" by "unexplained" as long as the real cause of a disease is not known.

Treatment of fatigue is discussed in chapter 5.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is shrouded in mystery. Other less accurate names used to describe this condition are ME syndrome, ME being an abbreviation of myalgic encephalomyelitis. 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.

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

References

1. d'Elia HF, Rehnberg E, Kvist G, *et al.* Fatigue and blood pressure in primary Sjogren's syndrome. *Scand J Rheumatol* 2008;37:284-92.
2. Ruiz-Iratorza G, Egurbide MV, Olivares N, *et al.* Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology (Oxford)* 2008;47:920-3.
3. Barendregt PJ, Visser MR, Smets EM, *et al.* Fatigue in primary Sjögren's syndrome. *Ann Rheum Dis* 1998 ;57:291-5.
4. Bax HI, Vriesendorp TM, Kallenberg CG, Kalk WW. Fatigue and immune activity in Sjögren's syndrome. *Ann Rheum Dis* 2002;61:284.
5. Godaert GL, Hartkamp A, Geenen R, *et al.* Fatigue in daily

- life in patients with primary Sjögren's syndrome and systemic lupus erythematosus. *Ann N Y Acad Sci* 2002;966:320-6.
6. Hartkamp A, Geenen R, Godaert GL, *et al.* Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. *Ann Rheum Dis* 2008;67:91-7.
7. Bowman SJ, Booth DA, Platts RG, *et al.* Measurement of fatigue and iscomfort in primary Sjögren's syndrome using a new questionnaire tool. *Rheumatology* 2004;43:758-64.
8. Varis K. Psychosomatic factors in gastrointestinal disorders. *Ann Clin Res* 1987;19:135-42.
9. Goodchild CE, Treharne GJ, Booth DA, Kitas GD, Bowman SJ. Measuring fatigue among women with Sjögren's syndrome or rheumatoid arthritis: a comparison of the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI). *Musculoskeletal Care* 2008;6:31-48.
10. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315-25.