



## Understanding Fatigue in Sjögren's Disease

**Taken from a presentation by Professor Fai Ng, Sjögren's UK Trustee and Professor of Rheumatology at Newcastle University.**

What is fatigue? Fatigue has been variously described as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion.

There are at least two types of fatigue - mental and physical and it is not unique to Sjögren's.

There are multiple possible mechanisms of fatigue in Sjögren's. Inflammation and fatigue are amongst the most studied biological processes.

'Sickness behaviour' is seen in both animals and humans. The term describes a constellation of symptoms including weakness, malaise, fatigue, aches, inability to concentrate and the development of depression and lethargy. There is some evidence that developmentally men, (because of rising testosterone levels in puberty enlarging the temperature-sensing area of the brain) are more sensitised to raised temperature and thus more symptomatic when unwell – providing a scientific explanation for 'man-flu'.

A raised body temperature is associated with an increased metabolic state.

Mice specifically bred to lack Interferon, IL-6 and TNF receptors display less sickness behaviour when infected than 'normal' animals. Patients receiving IFN treatment report fatigue. Disruption of the ACTH/cortisol/HPA axis may lead to fatigue.

Autonomic dysfunction may also be linked to fatigue. The autonomic nervous system controls involuntary bodily functions. Patients with fatigue report symptoms suggestive of autonomic dysfunction. Tests for this include tilt tests, sweat tests etc. POTS (Postural Orthostatic Tachycardia Syndrome) is seen in autonomic dysfunction and also in deconditioning.

When it comes to sleep, quality is as important as quantity. Non-restorative sleep, where patients have vivid dreams and wake frequently, is associated with fatigue.



MR spectroscopy is an experimental, non-invasive test which can demonstrate changes in brain tissue in those with chronic fatigue. Changes are also seen in patients with sleep disturbance.

A balance between oxidants and anti-oxidants may be important in maintaining bodily functions. Imbalances may lead to release of serotonin which is a neurotransmitter within the brain. Imbalance in serotonin levels may affect sleep, mood and fatigue.

Some patients may be more sensitive to fatigue than others. This might be genetically determined. Or it may be gene level activity being affected by other factors.

There are genetic differences in cytokines, neural transmitters and proteins that regulate circadian rhythm.

There are challenges in studying fatigue – for instance how do we accurately measure or quantify fatigue, there is often no pre-morbid evidence available and a large number of subjects need to be studied to draw any firm conclusions. Also fatigue is a complex outcome of many inputs.

Co-Enzyme Q10 is used by some patients as a treatment for fatigue although the evidence it works is sparse.

Data from the UKPSSR showed 33% ranked physical fatigue as their most disabling symptoms. 96% ranked physical or mental fatigue as the most or second most disabling symptoms.

Symptoms of fatigue are relatively stable over time.

Fatigue in Sjögren's may be multifactorial and due to associated or other conditions.

Fai hypothesised that there is a common underlying biological pathway for fatigue in Sjögren's.

Researchers have performed whole genome expression analysis on patients with Sjögren's and found no differences between those with significant fatigue and those without. However

their studies have identified 19 pathways where there was a difference in Sjögren's patients with and without fatigue. They also undertook serum cytokine profiling and measured levels of 24 different cytokines and looked at many other laboratory parameters and symptoms. Using this data they then predicted fatigue and compared this to actual fatigue – cytokine levels emerged as useful predictors of fatigue with low IFN (interferon) levels predicting higher fatigue, and low inflammation overall predicting higher fatigue levels. Interestingly although IFN levels are lower in those with higher fatigue they are still higher than healthy individuals.

Fatigue overlaps with pain and depressive symptoms making studying fatigue even more difficult.

Fai and his colleagues undertook a cluster analysis – to see if they could group symptoms together. They found some patterns and 4 distinct symptom groups which they described as:

- Low symptom burden
- High symptom burden
- Dryness dominant with fatigue
- Pain dominant with fatigue

These findings suggest that the biological mechanisms underpinning fatigue may be different for different individuals depending on other co-existing clinical features. And we hope these groupings (instead of investigating individual symptoms) may allow us to identify the biological mechanisms underpinning different 'types' of fatigue.

Are there any specific treatments for fatigue? To date there is no 'cure' for fatigue but some treatments are partially effective or show promise. These include hydroxychloroquine and biological therapies such as rituximab (promising phase 2 trials but disappointing phase 3 trials to date). A multidisciplinary therapy led intervention study in Newcastle has demonstrated improvements in fatigue scores suggesting that some patients do respond to multi-disciplinary approach which include activity management, correction of autonomic dysfunction if present, CBT-insomnia, graded exercise and mindfulness, tailored according to patient needs.

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Sjögren's Disease is the UK's second most common autoimmune rheumatic disease, yet the condition remains under recognised and frequently under treated. It does not command a high profile within the medical profession and the general public is largely unaware of the problems faced by sufferers. In reality, Sjögren's Disease is a debilitating, distressing and miserable condition.



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