Making sense of fatigue

Fatigue is a debilitating symptom that can affect all age groups impacting upon quality of life. The symptom of fatigue can occur in association with a wide range of chronic diseases (e.g. Parkinson’s disease, liver disease, diabetes), can be unexplained (chronic fatigue or idiopathic fatigue) or can occur in conjunction with a constellation of symptoms that form the syndrome of chronic fatigue syndrome (CFS) or myalgic encephalopathy (ME).

While some of the psychosocial correlates, antecedents and consequences of fatigue have been elucidated, our understanding of the biological basis for fatigue has lagged behind. This is not because fatigue is considered psychosocial, but rather a lack of appreciation that chronic diseases are associated with systemic symptoms such as fatigue. While there have been mixed and inconclusive findings of alteration in hypothalamus-pituitary adrenal axis function [1], other research in CFS/ME [2–5] and other fatigue-associated diseases such as Parkinson’s disease [6], multiple sclerosis [7] and autoimmune liver disease [8–11] confirm that fatigue arises, in a significant proportion of affected individuals, in association with abnormalities of sleep rhythm and dysregulation of the autonomic nervous system. Recognition of these biological associates is important as both sleep disturbance and autonomic dysfunction are potentially treatable in their own right and are associated with improvements in fatigue and quality of life [12,13]. Furthermore, sleep abnormalities and autonomic dysfunction are established risk factors for cardiovascular disease, particularly sudden cardiac death, an association that we have recently made in fatigue associated with the autoimmune liver disease primary biliary cirrhosis (PBC) [14]. This gives rise to the intriguing possibility that fatigue, in addition to its potential impact on quality of life, may contribute to morbidity and even early death in the more general population. Important recent work has suggested that fatigue is a generic symptom that arises with a specific phenotype across the spectrum of conditions where it presents [15]. This points towards a common pathophysiological pathway and potentially to generalized interventions for fatigue in the range of diseases in which it presents.

The extent and nature of the problem

Studies have confirmed that 25% of all general practitioner (GP) consultations are attributable to the symptom of fatigue with it being the main reason for GP attendance in 6.5% of consultations [16]. Community surveys have shown that fatigue is common in developed countries with a British survey of those attending general practice finding that 10.2% of men and 10.6% of women had had substantial fatigue for over a month [17]. Studies from the USA confirm that fatigue occurs in almost 40% of workers, resulting in lost productive time in 65% of these workers (compared to 26% in those without fatigue). Workers with fatigue cost employers $136 billion annually, an excess of $101 billion compared with workers without fatigue [18]. It was also noted that when fatigue co-occurred with other conditions, it increased the condition-specific lost productive time 3-fold. Despite its prevalence, surprisingly few large-scale studies have looked at the demographic, psychological and social associates of fatigue and none have looked at its biological associates.

Existing fatigue research

The largest population-based study to date in the UK [19] has confirmed that fatigue is closely associated with psychological morbidity and is best considered as a continuum that follows a classic bell-shaped curve distribution in the community. This means that there are few in the population who are never tired, and equally few who are severely disabled by fatigue, while in the middle, there is a large proportion of individuals who suffer from fatigue to varying degrees. What is unclear is whether the associated psychological morbidity is the cause or consequence of fatigue. Research to date has focussed on problematic fatigue, usually termed chronic fatigue. Some would argue that CFS/ME is a distinct clinical entity but we would suggest that CFS/ME is the extreme end of the chronic fatigue spectrum. Fatigue is known to be associated with a wide range of demographic, physical, emotional, personal, inter-personal and social variables.

Demographics

Fatigue becomes more prevalent with age [20], particularly in the older population who also suffer from chronic pain [21]. In addition, females are two to three times more likely to complain of fatigue than males [22], while fatigue is relatively rare prior to adolescence, it becomes more common afterwards with CFS/ME being the most common cause of long-term school absence in adolescents [23].

Physical factors

Several physical factors have been shown to predispose individuals to developing fatigue. Besides being associated with a wide range of chronic medical conditions,
including Parkinson’s disease, connective tissue disorders and anaemia, it is common post-operatively [24] and post-virally, particularly if the virus is associated with pre-morbid depression [25] or depression at the time of infection [26]. It is known to follow cessation of regular physical activity [27] and to be associated with lack of fitness and physical deconditioning [28]. A large twin study reports a ‘modest genetic component’ [29]. Most consistently, there is a high correlation with pain [30], although it is impossible, at present, to determine whether the relationship between these two factors is causative or associative.

**Mental health and emotional factors**

As with the pain literature, the direction of causality is difficult to ascertain in many of the studies currently in the literature, i.e. is emotional distress the cause, consequence or correlate of fatigue? Clearly, they are associated. Most consistently, there are clear associations between anxiety, depression, fatigue and other unexplained physical symptoms [22]. In the twin study of >7700 individual twins with a prevalence of ‘interfering fatigue’ of 9.4% [29], correlates fell into two distinct clusters, the first being depression, anxiety and neuroticism and the second being health beliefs about the danger of activity when symptomatic and alcohol problems. In one of the few large prospective studies that tracked the onset of fatigue [31], prior history of somatic symptoms was the single biggest predictor of unexplained fatigue, while there was a two-way relationship between depression and fatigue. One smaller study [27], in which normally active subjects ceased regular physical activity, found that fatigue was the first symptom to occur, preceding the later emotional distress.

**Social and work factors**

How fatigue is perceived by the diagnosing medical gaze may make a difference to its course. Being given the label ME appears to be associated with a significantly worse prognosis than that of post viral fatigue syndrome [32]. Work patterns, particularly shift work and lack of rest breaks, consistently emerge as pre-disposing people to fatigue [33] as do work situations of high demand and low control [34]. Social support and more say in work-related decisions are considered protective against fatigue. One large epidemiological study has suggested a U-shaped relationship between fatigue and social support with too little being associated with fatigue, but so was too much [35].

**Biological associates of fatigue—current research**

The medical literature investigating the biological basis of CFS/ME and fatigue in chronic diseases is extensive. Limitations notwithstanding, one consistent theme in this literature is that of vascular abnormalities and their regulation by the autonomic nervous system [2–6]. Over recent years, our group has been involved in a series of studies investigating the pathogenesis of fatigue, particularly in the autoimmune liver disease PBC [8–14]. Our studies have gone a long way to improving our understanding of the biological basis for fatigue in PBC, and we are now recognizing the long-term consequences and associations of fatigue, such as excess mortality related to sudden cardiac death and cognitive impairment. During these studies, we have recognized the contribution that two particular pathogenic factors make to the manifestation of the symptom of fatigue, namely autonomic nervous system dysregulation and sleep disturbance. In a wide range of chronic diseases and also in CFS/ME, we have shown strong correlations between fatigue severity and objective and subjective assessments of both autonomic function and excessive daytime sleepiness.

**Management of fatigue**

Fatigue is frequently considered as a ‘heart sink’ symptom by many clinicians. But it is important when considering subjective symptoms such as fatigue that patients have a positive consultation experience. Studies have shown that the majority of primary care physicians believe that fatigue arises as a consequence of psychological rather than physical factors, with those with fatigue having a negative consultation experience with those physicians from a psychological persuasion. Frequently, our patients are simply so relieved to talk to someone who ‘believes’ them and gain a huge amount from talking through their experiences with a clinician who apparently cares. So it is an important lesson, when faced with a patient who is complaining of fatigue to make sure that you do not fail before you begin. A structured approach to the assessment, investigation and management of fatigue is the way to achieve the greatest benefits for patients.

**Assessment**

The first thing to consider in any clinical evaluation of a patient complaining of fatigue is whether the symptom is secondary to an underlying condition. It is important to consider easily reversible causes of fatigue, such as anaemia, hypothyroidism, medication (e.g. beta blockers, anti-histamines), and whether a fatigue-associated chronic disease may be present (e.g. fatty liver disease, Parkinson’s disease, multiple sclerosis). Secondly, it is important to take the time to discuss the fatigue patients lifestyle including work and sleep patterns. Objective assessment is often valuable for patients and clinicians, so combining subjective evaluation with symptom assessment tools such as the fatigue impact scale together with activity monitoring can make visible the significant symptoms that affect an individual. Daytime sleepiness can be
quantified with the Epworth Sleepiness Scale (ESS) [36] with scores >10 being consistent with excessive daytime sleepiness. Autonomic symptom burden can be captured using simple validated tools such as the orthostatic grading scale (OGS) [37] or the more complex composite autonomic symptom scale [38,39]. Both have been validated for self-completion and against laboratory-based autonomic tests. In PBC, we have developed strategies that combine these assessment tools to detect the majority of fatigued patients with PBC. The diagnostic criterion of ESS >10 and OGS >4 is in use in our clinical practise and directs effective interventions that we are beginning to show reductions in fatigue [13, 40].

Management

Appropriate management of secondary causes of fatigue together with sleep and activity evaluation is essential. Our early case series of patients suggest that daytime sleepiness can be treated with the stimulant modafinil with the added benefit of improvements in fatigue in patients with PBC [12]. Randomized controlled trials have shown benefits for fatigue in multiple sclerosis and in series of patients with fatigue related to shift work. In autonomic dysfunction, simple strategies to expand volume are the mainstay of treatment initially using conservative measures followed if unsuccessful by treatment with the mineralocorticoid fludrocortisone or the alpha agonist midodrine.

In conclusion, fatigue is a real symptom that impacts significantly upon quality of life. It is increasingly being recognized as a complication of a large number of chronic diseases.

Taking a positive structured empathic approach to the quantification, investigation and management of fatigue will lead to significant benefits for patients, allowing them to life their lives to the best of their ability (Table 1).

### Table 1. Successful approach to managing fatigue

| Fatigue is usually ‘real’ in chronic disease: treat it as such. It is normally multi-factorial with different patients with the same symptom having different causes (and different responses to treatment) Treat the treatable, ameliorate the amelioratable but always support and understand (do not fail before you start) Take a structured approach Quantification is key |

### References