Fatigue in MS

Multiple sclerosis related fatigue

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Fatigue is often the most disabling symptom of MS

How we define fatigue remains as controversial today as it did 40 years ago: ''*True fatigue and....tiredness are plainly different.*''[1]. Fatigue is more than tiredness and has recently been referred to as ''*pathological exhaustion*''.[2] In this context the term ''pathological'' would, for example, classify the physical fatigue which athletes experience as part of voluntary effort as being abnormal. Fatigue must therefore surely be a normal phenomenon—a subjective feeling of tiredness or exhaustion which could refer to both physical (motor activities) and mental (cognitive or emotional) processes. Fatigue is only pathological if it is disabling—that is, if it affects a person's social, physical, and occupational wellbeing. For lack of a better definition the Centres for Disease Control and Prevention (CDC) defines ''*profound fatigue*'' and by implication ''*pathological fatigue*'' in the context of the chronic fatigue syndrome (CFS) as fatigue that ''*is not improved by bed rest and that may be worsened by physical or mental activity*''.[3] This definition appropriately excludes exercise induced or temperature dependent conduction block, a form of physical fatigue which occurs in subjects with demyelinating disease.

Approximately 80% of subjects with multiple sclerosis (MS) have pathological fatigue and in half these cases it is their most disabling symptom. In general, fatigue does not correlate with neurological impairment, physical disability, or the lesion load on conventional magnetic resonance imaging (MRI). In one study, subjects with ''benign MS'' had as much fatigue as those with non-benign MS.[4] Rarely, MS may present initially as chronic fatigue. In more recent studies a relation has been demonstrated between altered cerebral activation patterns[5] and the development of progressive brain atrophy[6] and fatigue. In the latter study the development of progressive brain atrophy was independent of disability, mood, or other MRI findings.[6] These observations question whether anatomical and physiological substrates underlie MS related fatigue.

One emerging hypothesis is that MS related fatigue is caused by ongoing inflammation. Fatigue that occurs as a result of acute infections can be reproduced by the administration of proinflammatory cytokines—for example, the type 1 interferons (α or β) or interleukin 2. The evolutionary benefits of fatigue in relation to systemic infection are obvious—in response to an infection the immune response triggers a behavioural response to maximise an animal's chance of recovery and hence of survival. Thus it is not surprising that fatigue is such a prominent symptom in chronic diseases associated with systemic inflammation. In rheumatoid arthritis, a systemic inflammatory disease without obvious CNS pathology, levels of acute phase proteins correlate with fatigue.[7] In MS, weak correlations between fatigue and markers of systemic inflammation have been reported.[4 8] Similarly, in this issue of the journal (***see pages 34–9***), Heesen *et al* report a weak association between fatigue and the stimulated whole blood production of the proinflammatory cytokines tumour necrosis factor α (TNFα) and interferon γ (IFNγ).[9] An important observation, however, is that MS related fatigue does not correlate with Gd enhancing lesions on MRI,[6 10] the most widely accepted marker of active inflammation in MS. These observations suggest that MS related fatigue is linked to peripheral rather than central inflammation. This may explain why treatment with IFNβ, a systemically administered cytokine that reduces MRI activity, is not associated with an improvement in fatigue scores.[11] How systemic inflammation induces fatigue is unknown, but the symptom may be mediated by proinflammatory cytokines, similar to the hypnotic effects of interleukin 1 and TNFα.[12]

Whether or not fatigue is a sensory percept is a moot point. Focal areas of the cerebral cortex or subcortical structures involved in the perception of fatigue have not been identified. On the other hand, fatigue and arousal may have a similar neuroanatomical basis. In arousal, subcortical systems integrate sensory and environmental information, which is processed and stimulates the cerebral cortex through the ascending reticular activating system. The latter hypothesis would explain how systemic inflammation induces fatigue.

An important caveat to the above observations and to the ongoing research into MS related fatigue is the lack of well validated outcome measures to quantify fatigue. The interpretation of fatigue by subjects responding to the most commonly used fatigue questionnaires may be context and disease specific. Work is therefore required to standardise the measurement of fatigue in MS and other conditions.

Uncertainties over the definition, pathogenesis, and measurement of MS related fatigue are clearly hampering the testing of specific therapeutic anti-fatigue strategies. There are, however, unproven strategies that could be tried to help ameliorate MS related fatigue. As fatigue appears to be related to mood and quality of life, it is important to address these issues at the outset. Similarly, it is important to exclude common medical conditions that could exacerbate fatigue—for example hypothyroidism—and to optimise the doses of drugs that are known to exacerbate fatigue. Non-pharmacological approaches for the specific management of fatigue include behavioural therapy, graded aerobic exercise programmes, energy conservation strategies, dietary advice, environmental cooling, and improvement in basic sleep hygiene. For subjects experiencing disabling fatigue, amantadine may be partially effective.[13] Despite its widespread use, modafinil has yet to be shown to be effective in MS related fatigue.[14 15] Antidepressant drugs, particularly serotonin and the noradrenaline reuptake inhibitors, are widely used, with little or no evidence to support their effectiveness in MS related fatigue. The use of stimulants—such as amphetamines, methylphenidate, and pemoline (discontinued in the UK)—in MS related fatigue cannot be sanctioned in view of their unproven efficacy and potential side effects.

If the findings of Heesen *et al* prove to be correct then targeting inflammation may be the most effective anti-fatigue strategy in MS. Glatiramer acetate, which has an impact on MS relapses similar to IFNβ but which is not associated with the flu-like symptoms, appears to have a positive impact on MS related fatigue.[11] Nataluzimab, a selective adhesion molecule antagonist which reduces the relapse rate in MS by more than 50%, markedly improved the perception of wellbeing (a crude index that includes fatigue) compared with placebo.[16]

It is important that we, as health care workers, should recognise and understand the impact that MS related fatigue

has on sufferers from MS, and be aware of the emerging evidence that at least a component of this complex symptom is linked to inflammatory disease activity and that strategies are emerging to manage fatigue more effectively.

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Yawning

"One person yawning sets off everyone else"

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The precise role of yawning in human physiology remains unclear

Yawning is a stereotyped behaviour present in most mammals from rodents to humans and has been described since antiquity. Hippocrates considered yawning to be an exhaustion of the fumes preceding fever. Modern medicine did not pay much attention to it until the 1980s, when, with advances in neuropharmacology, yawning proved to be a valuable tool for the assessing dopaminergic activity and the pharmacological properties of new drugs. However, its precise role in human physiology is still unknown and its mechanisms remain unclear. The paper by Cattaneo *et al* (***see pages 98–100***) reports two cases of pathological yawning as the earliest symptom of brain stem infarction which introduces new arguments for locating this neuronal network in the lower brain stem.

Yawning occurs after waking up, before eating, before sleeping, and in passive activities when it is necessary to maintain a certain level of vigilance.[1] It is then followed by an acceleration of the electroencephalographic rhythms. It does not serve a primary respiratory function and it clearly has a non-verbal communicative status. Nevertheless, it is also a clinical sign in intracranial hypertension, migraine, or iatrogenic side effects of dopaminergic drugs and serotonin reuptake inhibitors.[2] In basal ganglia disorders, yawning is reduced in patients with Parkinson's disease, and occurs more often in patients with Huntington's disease and supranuclear palsy than in controls. In healthy volunteers, apomorphine induces yawning which is also observed at the beginning of the "on" periods in Parkinson's disease.[2]

The anatomical structures known to be implicated in the occurrence and control of yawning are the paraventricular nucleus of the hypothalamus (PVN), the hippocampus, the reticular formation, the neostriatum, and the cranial (V, VII, IX, X, XI, XII), cervical (C1–C4), and dorsal nerves. Yawning is probably a reflex answer of the brain stem reticular formation aimed to increase the cortical level of vigilance. Dopamine and oxytocin are the main neurotransmitters implicated in its modulation. Indeed yawning induces sensory efferents from the terminals of the fifth facial nerve to the reticular formation or the PVN through the spinothalamic and hypothalamic tracts. Stimulation of the dopamine D2 receptors of the PVN activates the oxytocin neurones that project either to the pons (reticular formation, locus coeruleus), to the hippocampus, to the insula, or to the orbitofrontal cortex, leading to the transient feeling of wellbeing that follows yawning. This pathway is modulated by acetylcholine, serotonin, opioid peptides, sexual hormones, and orexin. The paper by Cattaneo *et al* provides important data on the crucial role of the lower brain stem.

Contagious yawning is an even more intriguing phenomenon. It is triggered by seeing, hearing, or even thinking about someone else yawning. Contagious yawning does not occur in species that do not recognise themselves in mirrors or in infants younger than two years old. The phenomenon has been investigated with functional magnetic resonance imaging,[3] which implicated the precuneus or the posterior cingulate regions, functional regions associated with the identification of self referent information, a primitive form of empathy. Further studies are needed before conclusions can be drawn.

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