Fatigue after stroke

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Fatigue is a common symptom after stroke. It is not invariably related to stroke severity and can occur in the absence of depression. It is one of the most troublesome symptoms for many patients and yet nothing is known of its causation. There are no specific treatments. This article assesses the available literature in the context of what is known about fatigue in other disorders. Post-stroke fatigue may be a manifestation of sickness behavior, mediated through the central effects of the cytokine interleukin-1, perhaps via effects on glutamate neurotransmission. Possible therapeutic strategies are discussed which might be a logical basis from which to plan randomized control trials.

Keywords: fatigue, interleukin-1, proinflammatory cytokines, sickness behavior, stroke

Following stroke, approximately a third of patients die, a third recover and a third remain significantly disabled. Even those who recover physically may be left with significant emotional and psychologic dysfunction – including anxiety, readjustment reactions and depression. One common but often overlooked symptom is fatigue. This may occur soon or late after stroke, may be completely debilitating, and does not seem to be related to stroke severity [1,2]. Fatigue may have significant effects on quality of life (QoL) and affect the chance of a patient returning to work [3]. Despite this, it is rarely mentioned in the stroke literature. For example, it is not referred to in the National Stroke Guidelines [101] and there is scant reference to it in one of the most commonly used stroke textbooks [4]. It needs to be recognized by health and social care teams in both primary and secondary care. Warning the patient and their family that fatigue is a likely consequence of even mild stroke is important as it can be a worrisome and debilitating symptom.

Definition of fatigue

There is no exact definition of fatigue because of its inherent subjectivity. It may usefully be described as difficulty initiating or sustaining voluntary activities [5]. It occurs in response to activities requiring a sustained effort, or as a primary state associated with a sense of near-constant exhaustion which differentiates it from the universal experience of intermittent tiredness.

Fatigue in medical conditions

Fatigue is a common feature of many chronic disorders. Two-thirds of patients with multiple sclerosis report excessive fatigue [6]. It is a common and disabling symptom of Parkinson's disease [7,8] and of systemic lupus [9]. More than 90% of patients with poliomyelitis develop a delayed syndrome of post-myelitis fatigue [10]. Fatigue is the most prevalent symptom of patients with cancer who receive radiation, cytotoxic or other therapies [11], and it may persist for years after the cessation of treatment [12]. It also occurs following infectious disease, classically infectious mononucleosis, and can persist for years following diagnosis [13].

Fatigue after stroke

Fatigue after stroke is a common phenomenon – many patients describe it as the most difficult symptom that they have to cope with [3]. It is an independent predictor of dependence in activities of daily living and may be associated with higher mortality. It contributes to a decline in QoL after discharge from hospital in some patients with stroke. It may particularly affect those with good physical recovery, impairing or even preventing their ability to return to normal life. A qualitative study of young peoples' experiences of stroke rehabilitation emphasized the negative effect of fatigue on their attempts to return to normality [14]. A further qualitative study of older stroke patients concluded that fatigue significantly affected performance in a variety of activities as well as their independence [15].

Depression is associated with fatigue (indeed it is a component in most depression scales) but is not a prerequisite for it. In a study of patients following stroke, 51% of stroke patients compared with 16% of controls experienced severe fatigue, while 20 and 16% had elevated depression scores respectievly [1]. At

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15 months post-stroke 57% of 220 patients studied had post-stroke fatigue – a significant proportion reported fatigue prior to the stroke [16]. At 3 to 13 months after stroke, Ingles found fatigue without depression in 39% of patients [17]. Even 2 years after stroke the incidence of fatigue remained high. A total of 10% of responders to the question 'Do you feel tired?' responded 'always' and 29.2% 'sometimes', 2 years after stroke [18]. Risk factors for post-stroke fatigue in this study included increasing age and pre-stroke morbidity. Fatigue was a predictor for worse outcome, including more dependence in activities of daily living and worse general health, independently of depression. It was also a predictor for death independently of depression and other predictors of survival.

Functional outcome using the health-related QoL score (SF36) shows deterioration in QoL for some domains, particularly emotional ones following discharge and for up to 3 years after stroke in another follow-up study [19]. A small pilot study of 20 patients assessed at a mean of 63 days post stroke found that 40% had significant fatigue, which in many cases interfered with their ability to participate in physiotherapy sessions [20].

Fatigue following stroke is not necessarily associated with severity of physical impairment. A study of patients with mild stroke (Oxford Handicap Score 0–1) 1 year after stroke found fatigue in 72% of patients, with adverse consequences for QoL and the ability to self care [21]. In patients with subarachnoid hemorrhage who had made a good neurologic recovery (Glasgow outcome Score 4–5 at discharge from hospital) followed up at 3, 9 and 18 months post discharge, 58% reported severe fatigue at 3 months and 17% at 9 months, with little improvement by 18 months [22]. A population-based study of 232 young adults (15–49 years) at a mean follow-up of 6 years after ischemic stroke reported fatigue. This was independently associated in multivariate analyses with impaired functional state (higher modified Rankin score) and with basilar artery infarction [23].

Measurement of fatigue

The measurement of fatigue after stroke is difficult because of the subjective nature of the symptoms and the difficulties controlling for coexistent physical impairments and depression. One option is simply to ask patients whether they feel tired – for example a three-point scale of physical and/or mental tiredness (where 0 = none, 1 = mild/moderate and 2 = severe) [21]. The Health-Related QoL scale (HR-QoL) has a subscale for vitality which assesses fatigue [19].

One stroke-specific QoL measure has been developed with input from patients – this includes a fatigue subscale consisting of three questions [24].

A number of scales have been developed for the assessment of fatigue in other disorders, particularly in cancer [25–27]. Some scales test general fatigue [28], others mental [29] or physical fatigue (e.g., the fatigue subscale of the Checklist Individual Strength used in Van der Werf's study). In post-stroke fatigue there are likely to be a number of contributing factors which are both physical and psychologic. A multidimensional instrument is therefore probably required [30].

An international classification of diseases (ICD) criteria set has been developed for the diagnosis of cancer-related fatigue [102]. These include physical (general weakness, limb heaviness) and psychologic symptoms (emotional reactivity, perceived need to struggle to overcome activity) which cause clinically significant distress or impairment in social or other functioning. Similar criteria might be useful in post-stroke fatigue as they are multidimensional and applicable to a group of patients with other physical symptoms.

Mechanisms of fatigue

Fatigue is a characteristic symptom of depression, and patients may be depressed by fatigue, but it is clear from observational studies that post-stroke fatigue can exist in the absence of depression. The frequency of fatigue in physical disorders such as infections, multiple sclerosis and cancer suggests that there may be common underlying mechanisms. Sickness behavior refers to a coordinated set of subjective behavior and physiologic symptoms that characteristically occur in infection including; fatigue, malaise, nausea, anorexia and aching joints. These symptoms are part of an organized adaptive survival strategy that allows the organism to deal most effectively with infection. The mediators of these changes are the proinflammatory cytokines, particularly interleukin (IL)-1. The naturally occurring antagonist of IL-1, IL-1 receptor antagonist (IL-1ra) attenuates sickness behavior in experimental models as measured by reduction in social interaction or food intake [31]. Activation of the brain cytokine system in a noncompromized individual allows the organism to respond in a coordinated way to

infectious pathogens. However, there is good evidence to suggest that excessive activation of the brain cytokine system, for example by the cytokines released by cancer cells or induced by chemotherapy and radiotherapy, may be responsible for many symptoms of cancer including fatigue [32]. In other disorders associated with chronic inflammation, central cytokines may also be responsible for mood disorders and fatigue. Multiple sclerosis for example is associated with brain cytokine changes. Stroke is associated with inflammation [33] and IL-1 is clearly implicated in the pathogenesis of damage following ischemia. Inflammatory markers are elevated in plasma for some months after stroke [34] and correlate with stroke severity [35]. Activation of brain cytokines with a form of sickness behavior may be responsible for fatigue after stroke. Proinflammatory cytokines impair astroglial glutamate uptake and clearance. Glutamate signaling is essential for information processing and one mechanism suggested through which cytokines might contribute to mental fatigue is through dynamic alterations in glutamate activity [36].

Imaging in fatigue

In order to determine whether fatigue is associated with particular brain regions, a prospective magnetic resonance (MR) study would be required in a large number of patients, followed-up to determine the association between regional damage and the presence of fatigue. MR spectroscopy (MRS) of the brain and muscle has been used in chronic fatigue syndrome showing abnormal muscle metabolism in some patients with early intracellular acidosis and changes in regional *N*-acetyl-aspartate peaks [37]. The significance of this is unclear but may suggest changes in cell membrane turnover. Reduced gray matter volume has also been found in the prefrontal cortex in chronic fatigue patients [38]. There are a number of techniques being developed for the imaging of brain inflammation [39,40] which could be of value in determining the role of proinflammatory cytokines in fatigue. MRS techniques can be used to measure regional glutamate concentrations [41]. If successful, brain imaging could provide a surrogate outcome for therapeutic studies in stroke, prior to large randomized controlled trials.

Potential interventions in the management of fatigue

A number of interventions have been proposed for the management of fatigue in cancer and chronic fatigue syndrome. In the absence of a clearly defined mechanism, the approach to management needs to be general. Some of these treatment options might be applicable to post-stroke fatigue.

Physical activity

Graded aerobic exercise is associated with improvements in physical work capacity, and some psychologic and cognitive variables in patients with chronic fatigue syndrome [42,43]. Exercise training leads to decreased fatigue and reduced effort [44]. Significantly lower levels of fatigue are found in cancer patients who take exercise, although these studies are mainly in patients with breast cancer [11]. Most exercise studied was aerobic with walking or treadmill protocols [45]. Patients undergoing radiotherapy for prostate cancer advised to rest if they became fatigued, had a significant deterioration in physical function and a significant increase in fatigue compared with an exercise intervention group [46]. Exercise might be difficult for stroke patients with physical disability but chair-based or other suitable exercise programs could be developed and mobile patients could be encouraged to take up regular exercise.

Rest & sleep

It is not known whether additional rest and sleep has any effect on fatigue. Patients with cancer fatigue report sleep disturbances with poor quality of sleep and stroke patients anecdotally report that they wake unrefreshed from sleep. It would seem likely that good sleep patterns should be beneficial and patients can be encouraged to try to avoid excessive daytime sleeping.

Cognitive interventions

A brief psychoeducational intervention has been shown to improve outcome in chronic fatigue syndrome [47,48] and in the fatigue of infectious mononucleosis [49] and systemic lupus [50]. A number of interventions to increase psychosocial support have been assessed in cancer. These interventions (support groups, counseling and comprehensive coping-strategy programs) have tended to demonstrate a reduction in fatigue and distress [11]. Simply warning patients and carers about the likelihood of post-stroke fatigue may also be of benefit.

Pharmacologic interventions

No specific pharmacologic interventions have shown to be of conclusive benefit in chronic fatigue syndrome [51]. Cancer-related fatigue has been targeted with treatments specific to the type of tumor (e.g., erythropoietin for fatigue in

cancer-related anemia) and megestrol in breast cancer. Psychostimulants have been used in fatigue associated with HIV-1 infection [52] and multiple sclerosis [53]. There have been no published trials in post-stroke fatigue.

Pharmacologic treatment of pain, spasticity and poor sleep are important as these affect the severity of fatigue. Central post-stroke pain typically disturbs sleep and will contribute to fatigue, therefore appropriate treatment may help. However, there are no specific treatments for post-stroke fatigue *per se*. The most logical pharmacologic approach to post-stroke fatigue would be an agent that acts on IL-1 in the brain to reduce the symptoms of sickness behavior. IL-1ra is undergoing trials in acute stroke [54] and might benefit post-stroke fatigue – other anti-inflammatory agents might theoretically be of value.

Highlights

- Fatigue following stroke is common.
- Post-stroke fatigue can hinder the patient's rehabilitation.
- Post-stroke fatigue may be due to an inflammatory response related to interleukin-1.
- The treatment options for post-stroke fatigue are limited.
- Further research is required to accertain prevalence and thus devise appropriate therapeutic managements strategies.

Expert commentary & outlook

Fatigue is common and disabling. The exact prevalence of fatigue in those with stroke is uncertain, but may be as high as 70%. As yet, the mechanism is poorly understood and its management even less so. Pharmacologic agents have been tried in other medical conditions, but as yet none have a license in stroke. At this time, IL-1 would appear to be the most likely mechanism associated with fatigue, suggesting a possible therapeutic approach.

Further work is required to describe the scale of the problem in all stroke patients irrespective of age, and randomiszd controlled trials are needed to investigate possible therapeutic agents, such as those that have been tried in multiple sclerosis and IL-1 antagonists.

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