Post-Stroke Fatigue: Epidemiology, Clinical Characteristics and Treatment

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Key Words

Fatigue · Stroke · Depression · Asthenia

Abstract

Fatigue is a disabling and persistent symptom affecting many stroke survivors and is a predictor for death after stroke onset. Post-stroke fatigue is a multidimensional motor-perceptive, emotional and cognitive experience that has become of interest for stroke researchers only in the recent past. More studies are still needed to understand the pathophysiology, clinical characteristics, associated factors and best treatment strategy. The aim of this narrative review was to provide a comprehensive knowledge, from current literature, regarding the epidemiology, clinical characteristics and treatment of fatigue in order to provide physicians with better tools for treating this debilitating symptom that worsens outcome.

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Introduction

Post-stroke fatigue is described as ‘a feeling of early exhaustion with weariness, lack of energy and aversion to effort that develops during physical or mental activity and is usually not ameliorated by rest’ [1].

Fatigue is a multidimensional motor-perceptive, emotional and cognitive experience [2].

Fatigue can be classified as either objective or subjective; *objective fatigue* is defined as the observable and measurable decrement in performance occurring with the repetition of a physical or mental task, while *subjective fatigue* is a feeling of early exhaustion, weariness and aversion to effort [3].

Post-stroke fatigue is generally thought to be a primary fatigue, but many researchers have proposed several contributing factors specific to post-stroke fatigue, such as de-conditioning, physical impairment, disuse, sleep disorders, medications side effects and depression [4].

Methods

A computer-aided search in Medline was performed on June 6, 2013, which was later updated in October 2013 using the keywords ‘fatigue’, ‘stroke’, ‘depression’, ‘asthenia’.

The search retrieved 69 publications. Two authors read every abstract and obtained the full text of paper that were deemed interesting; reference lists of the retrieved articles were scrutinized for potentially relevant studies.

We excluded case reports, abstracts as well as articles not written in English and articles not published in peer-

reviewed journals. Moreover, we also excluded studies having a few patients enrolled.

Overall, 62 articles were read by the three authors in order to provide a narrative review of the epidemiology, clinical characteristics and treatment for post-stroke fatigue.

Epidemiology

Fatigue is among the most prevalent symptoms after stroke and is an important predictor for death after stroke onset [5]. The frequency of post-stroke fatigue ranges from 29% to 77% [5–9]. This large variability across studies is due to two known reasons. The first reason is that fatigue is difficult to define, characterise and measure [10]. In fact, methodological differences among studies include different definitions of fatigue, different inclusion criteria and different fatigue scales [2, 11].

No scales have been developed specifically for measuring fatigue after stroke. The most frequently used instruments for evaluating fatigue include the Fatigue Severity Scale (FSS), SF-36/12 (vitality subscale), the Profile of Mood States (POMS), the Fatigue Assessment Scale (FAS), and the Multidimensional Fatigue Symptom Inventory (MFIS). Of these, FSS is the most frequently used in stroke studies due to its high internal consistency. All of the scales lack a cut-off point. In this way it is difficult to determine the absolute degree of prevalence [9].

Second, these diverse levels of prevalence have been most likely due to the varying times of assessment. Yet, even in this context, data are scarce and contradictory. Christensen et al. [11] reported pathological fatigue in 59, 44, 38 and 40% of stroke patients at 10 days, 3 months, 1 and 2 years respectively, following the onset of stroke. Another study, found that the prevalence of post-stroke fatigue was 35% two months after stroke and 33% at 1.5 years post-stroke [12]. Radman et al. [13] reported similar results after 6 and 12 months following a minor stroke: 30.5 and 34.7%, respectively. Another longitudinal study showed an increased percentage of self-rated fatigue at admission as well as 6-month and 1-year follow-ups; 51.5, 64.1 and 69.5%, respectively [14].

Clinical Characteristics

Descriptions of pathological fatigue have included different dimensions of the phenomenon, with problems related to self-control and emotional instability, reduced

mental capacity and perceived reduction in energy needed for daily activities such as reading and participating in physical or social activities [7]. It is generally qualitatively different from the fatigue experienced before stroke and can be exacerbated by stress and physical exercise, and responds well to rest, sleep and low temperature [2]. This type of fatigue is more commonly known as exertion fatigue. Exertion fatigue is acute in nature, with a rapid onset, short duration and short recovery period [15], commonly experienced after intense physical exertion or use of mental effort [16, 17]. Other described subtypes of fatigue include mental fatigue and psychological fatigue. Mental fatigue appears with cognitively demanding tasks, while psychological fatigue is associated with lack of interest or poor motivation [3]. These subtypes of fatigue are not mutually exclusive; if exertion fatigue is more prevalent in patients with stroke, mental or psychological fatigue is more prevalent in patients with other neurological diseases including multiple sclerosis [2, 18].

Indeed, Tseng et al. [15] reported that aerobic fitness and depression are strong independent predictors of exertion fatigue and chronic fatigue in post-stroke, respectively suggesting that exertion fatigue and chronic fatigue are distinct.

Predisposing and Associated Factors

Stroke Type, Stroke Side and Stroke Location

Associations between fatigue and stroke features remain controversial.

Moreover, the claim on the part of the patients that fatigue after stroke is unlike anything ever experienced before [19], supports the idea that there may be an underlying association between fatigue and brain lesion size and its location.

Some studies have reported no relationship between fatigue and stroke location or fatigue and stroke type [5, 7, 8, 11, 13, 20–26]. A study has reported a relationship between the number of strokes and fatigue, reporting a lower proportion of fatigue among patients who had a first stroke compared with those having recurrent strokes [5].

Regarding pathological type of stroke and fatigue, only one study in literature has reported that fatigue is more severe after ischaemic stroke than after intracerebral haemorrhage [27].

Conversely, studies have suggested an association between post-stroke fatigue and stroke side and location. In

a study in patients with minor infarct, there was no observed correlation between infarct and fatigue severity scores, except for a tendency toward left parietal lesions [13].

Tang et al. [28] found that fatigue after stroke has been associated with acute infarcts in the basal ganglia and internal capsule detected on MRI, whereas Snaphaan et al. [12] observed that fatigue after stroke has been more common in patients with infratentorial lesions detected on either CT or MRI. Similar findings have been reported by two studies observing a relationship between fatigue and lesions in the posterior circulation territory, defined as either brainstem or thalamic stroke [29] basilar artery infarction [26]. In this regard, a recent study [22] even if it revealed no CT predictors for fatigue at 1 month after stroke, using the OCSF classification [30] as an alternative indicator of lesion location, indicated that patients with POCS had higher fatigue scores than those with other subtypes. Some authors have hypothesised that damage to the ascending reticular activating system in the brainstem may lead to mild impairment in arousal, changes in attention and subsequent development of fatigue [1], whereas others have supposed that the disruption of serotonergic pathways in the brainstem is another potential mechanism of fatigue after stroke [31].

Neuroradiologic Findings

Even if a study comparing the severity of cerebral atrophy and white matter lesions in patients with or without fatigue after stroke did not report any association [12], a recent study has described that severe leucoaraiosis on CT was predictive for developing fatigue 1 year after haemorrhage [32]. Likewise, Naess et al. [33] have reported that the presence of leucoaraiosis on CT was independently associated with post-stroke fatigue in patients with ischaemic or haemorrhagic injury. These findings are consistent with the hypothesis that neuroanatomical changes may play a role in the development of fatigue.

Motor Recovery and Residual Disability

Patients who feel that they have not made a full recovery are significantly more likely to be fatigued than those who make a full recovery. However, in patients with excellent neurological and neuropsychological recovery, as in patients with minor stroke or TIA, post-stroke fatigue may be the only persisting sequela, which may severely limit a complete recovery of their previous level of functioning. Even if the prevalence of fatigue after a minor stroke is usually higher than after TIA, fatigue can also be present after a transient neurological deficit. In these

cases, the influence of additional depressive and anxious factors on the impact of fatigue should be addressed [1]. However, Winward et al. [34] have described that patients with minor stroke reported significantly higher levels of fatigue at 6-month follow-up than those with TIA and this difference was independent of measured potential confounders for fatigue, including anxiety, depression, recent life events, relevant blood tests, and medication; this suggests that an excess of fatigue in patients with minor stroke indicates a causal association between fatigue and cerebrovascular accident. Although fatigue can be related to increased physical efforts associated with severe neurological deficits, the presence of fatigue in stroke patients with little or no motor deficit suggests that this excess of fatigue, compared with TIA patients, is most likely attributable to central mechanisms.

Functional neuroimaging studies have reported that physical activity is associated with activation of the prefrontal brain as well as the insula and anterior cingulate cortex [35]. These areas have been implicated in the development of tiredness after stroke [36]. Thus, physical activity, by activating the prefrontal circuits, may improve attention and therefore reduce fatigue. One plausible model for post-stroke fatigue is that reduced physical activity after stroke leads to physical de-conditioning and in turn exertional fatigue (neuromuscular fatigue), which then is responsible for the avoidance of physical activity, contributing to the development of chronic (cognitive) fatigue [37].

There are multiple underlying mechanisms by which exercise may improve post-stroke fatigue: exercise can increase the cerebral blood flow by activating the sympathetic nervous system, whereas on a molecular level, it is thought to change the functioning of neurotransmitters, which has been suggested for its role in the development of fatigue [38, 39].

Depression

A strong relationship between depression and post-stroke fatigue has been described and the presence of fatigue indeed constitutes one of the criteria for depression in most scales [3]. Moreover, depression is considered one of the most critical concomitant post-stroke symptoms associated with fatigue, making it difficult to differentiate between them as independent conditions.

In a study [40] of 200 Italian patients with first-ever stroke surveyed for depression three months after their stroke, their scores for fatigue or loss of energy tended to be significantly higher among patients who had a minor

depressive disorder compared to those without any depressive disorder. Similar findings were found in a Belgian study [41] that reported that reduced appetite, psychomotor retardation, and fatigue contributed significantly to identifying patients who had post-stroke depression. Likewise, a relationship between depression and high levels of fatigue has been reported in several other studies [5, 8, 26, 42, 43]. Carlsson et al. [7] concluded that the odds ratio for having fatigue one year after stroke in the presence of depression, was 3.2 (95% confidence interval: 1.7–6.0).

However, post-stroke fatigue can also occur in the absence of depression, with the latter found to be independent of fatigue in stroke survivors [20, 21]. Van der Werf et al. [6] found that only 38% of patients with severe fatigue were also depressed. Ingles et al. [20] reported similar findings with 29% of patients having both symptoms.

Cognitive Impairment

Cognitive impairment has been found to worsen fatigue after subarachnoid haemorrhage [44, 45] and brain injuries; nonetheless, this association has received little attention. Additionally, in a sub-study on quality of life of the International Stroke trial, Mead and colleagues found that a worse mental health score and worse emotional role function measured with SF-36 and increasing age were significantly associated with fatigue [23]. Conversely, a long-term study [26] has reported no association between fatigue and cognitive impairment, but this result could be explained by the fact that they used only the Mini-Mental State Examination, which does not assess attention or executive function.

Gender

Several studies of fatigue in general population have reported a higher proportion of fatigue among women [46–48]. However, there is conflicting evidence on a relationship between gender and post-stroke fatigue. In fact, some researchers have suggested that there are no differences between the sexes [12, 25, 26], while some other studies have reported a higher proportion of post-stroke fatigue among women [20, 22, 23]. This sex disparity could be explained by endocrine and stress-related factors.

Time Course of Fatigue and Influence on Outcome

In a Danish study [11] analysing the course of fatigue over a two-year follow-up after first-ever stroke, the post-stroke fatigue level was seen to decrease during the first three months after hospital discharge. This situation re-

mained unchanged for the next 2 years of follow-up. Different findings have come from a study by Schepers et al. [8] who have reported an increase in the prevalence of fatigue during the first year after stroke. This difference could have been explained by the high prevalence of depression in the Schepers's study, which could have influenced the time course of fatigue.

Regarding the duration of pathological fatigue after stroke, this could become chronic and be present several years after stroke onset-up to 40% after two years [11].

The initial level of fatigue is the main determinant of increasing fatigue over time [9] and this being the case, targeting fatigue soon after stroke can help in preventing its persistence.

Several studies have reported that post-stroke fatigue is an independent predictor of shorter survival [5, 23], institutionalization [5, 21], poorer functional outcome [11] and greater dependency for activities of daily living (ADLs) and instrumental activities of daily living (IADLs) [43]. Moreover, in young patients, fatigue appears to be a determinant of not being able to resume paid work following stroke, independently of physical disability or cognitive deficit [49].

Treatment

Fatigue following stroke is a multidimensional symptom and may have several causative factors. Currently, there are no evidence-based interventions that can successfully prevent and treat post-stroke fatigue. However, pharmacological, physical and psychological treatments are used to alleviate fatigue. Furthermore, environmental suggestions can also provide benefit. A multidisciplinary approach that targets both the physical as well as the cognitive aspects of fatigue is needed [50].

Pharmacological Treatment

Even if depression and fatigue are commonly dissociated and sometimes anxiety and depression are known to be consequences rather than causative factors of fatigue, anti-depressant or counselling may address the mental aspects of fatigue [51].

Choi-Kwon et al. [42] evaluated the therapeutic effects of fluoxetine 20 mg/day on fatigue and other emotional disturbances in a placebo-controlled, double-blind trial including 83 outpatients with post-stroke emotional disturbances, at a mean of 14 months after stroke onset. Fatigue was evaluated by the Fatigue Severity Scale (FSS) and the Visual Analogue Scale (VAS) at baseline, three

months and six months after the start of treatment. Fluoxetine resulted being ineffective on fatigue after stroke, but it seemed to decrease depressive symptoms, suggesting that serotonergic system dysfunction is not a potential mechanism for post-stroke fatigue.

Treatment of pain may help patients because it allows for the participation in exercises and improves mood disturbance related to pain [51].

Sleep disturbances are coexisting symptoms of post-stroke fatigue, as reported in various studies [25, 52, 53]. In some of these individuals, sleep apnea has been diagnosed. However, an improvement in sleep disordered breathing (with a CPAP) does not seem to be effective in relieving post-stroke fatigue, unless accompanied by symptomatic sleep apnea syndrome [54].

Physical Treatment

Graded physical activity programs have been suggested for their contribution to the treatment of post-stroke fatigue. This is based upon the fact that exercise improves both physical and functional outcomes and therein reduces fatigue; as has been reported for medical conditions including cancer and multiple sclerosis [55–58].

Observational studies of stroke patients have reported that most patients are inactive during their hospital stays in both acute and rehabilitation wards. For these patients, graded physical activity programs have been recommended in order to help them gradually increase physical strength without aggravating distressing symptoms [59].

A cross-sectional study has reported that higher levels of fitness (measured using a maximal effort graded exercise test (V02 peak) using a stepping ergometer) were significantly associated with less exertion fatigue ($p < 0.01$); in the absence of an association between fitness and chronic fatigue [15].

A recent multicenter, randomized, controlled trial has indicated that a graded activity training programme plus cognitive therapy over a 12-week period leads to a greater reduction in persistent post-stroke fatigue compared to cognitive therapy alone. This reduction has been reported to remain stable at 6 month-follow-up producing an overall better functional health status, characterized by fewer symptoms of depression, and improvements in both sleep and physical endurance [44].

Psychological Treatment

Cognitive compensation strategies that circumvent the limited energetic resources available to patients suffering from post-stroke fatigue might also be beneficial.

These compensation strategies require enhanced planning and variation of activities to foster a more regular pattern of activities and rest [60]. An augmented form of cognitive behavioural therapy, as that proposed by Broomfield et al. [61] for post-stroke depression, is a good starting point for addressing these issues. These therapies take into account cognitive deficits and therefore might aid in fostering the behavioural changes needed to apply compensation strategies.

Environmental Suggestions

Environmental suggestions for improving in-hospital fatigue include regular access to fresh air, a home-like environment, good personal attention as well as access to communicative vehicles such as television, Internet and ward activities [62]. Many patients have reported disturbed sleep while in hospital due to hospital rhythms. Changes in the hospital living conditions could improve fatigue post-stroke.

Out-of-hospital recommendations include [51]: the encouragement of physical activity, proper nutrition, as well as adequate rest and relaxation.

Conclusions

Post-stroke fatigue is a common, complex, multi-factorial syndrome that is poorly understood regarding its pathophysiology, clinical characteristics and associated factors. Our review has found that there is a paucity of studies that have examined and sought to determine new intervention strategies for post-stroke fatigue. This indicates that currently there is a low level of attention paid to a post-stroke symptom, which is experienced by most post-stroke patients, greatly reducing the quality of life.

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