

## Post-Stroke Fatigue: Difficulties in Measurement and Treatment

Ank A Agarwal<sup>\*1</sup>, Akshay Bhamidipati<sup>2\*</sup>, Karan Patel<sup>3</sup>, Sean Bunachita<sup>4</sup>, Aakshi Agarwal<sup>5</sup>, Aaron Lyon<sup>6</sup>, Abhishek Puppala<sup>7</sup>, Amrutha Vellanki<sup>8</sup>, Arun Vellanki<sup>9</sup> and Vahini Srikakulapu<sup>10</sup>

<sup>1</sup>Medicine: Johns Hopkins University School of Medicine

<sup>2</sup>Medicine: Vanderbilt University School of Medicine

<sup>3</sup>Medicine: Cooper Medical School of Rowan University

<sup>4</sup>Molecular and Cellular Biology: Johns Hopkins University

<sup>5</sup>Molecular, Cellular, Developmental Biology: Yale University

<sup>6</sup>Biology: Brigham Young University-Idaho, Rexburg, USA

<sup>7</sup>Biology: Baylor University

<sup>8</sup>College of Science: Virginia Polytechnic Institute and State University

<sup>9</sup>College of Humanities and Science: Virginia Commonwealth University

<sup>10</sup>College of Health and Human Performance: University of Florida

### ABSTRACT

Post-stroke fatigue (PSF) affects millions of patients worldwide. It is categorized by debilitating fatigue and lack of motivation pervading numerous aspects of daily life. These difficulties affect patients physically, mentally, socially, and emotionally. Current measurements show that anywhere from 25% to 75% of the 17 million people globally who suffer a first-time stroke every year may also suffer from post-stroke fatigue. However, measuring post-stroke fatigue is fraught with numerous issues.

Researchers differ in their specific definitions of the condition, and there are various scales used to measure the severity of this fatigue. Moreover, many studies exclude patients in measurement if they have comorbidities such as depression, resulting in an added measure of complexity for comparing and creating meaningful conclusions. Post-stroke fatigue also has limited treatment options, many of which are limited in efficacy at best. Current efforts aim to treat the condition from a variety of lenses, including pharmacological, physical, psychological, and environmental. However, the best interventions are yet to be developed and will likely arise from improved understanding of post-stroke fatigue etiology and associated factors. Herein, we present a brief review of the difficulties in measuring stroke prevalence and treating the condition.

### \*Corresponding author

Akshay Bhamidipati, Medicine: Vanderbilt University School of Medicine 1161 21<sup>st</sup> Ave S # D3300, Nashville, TN 37232. E-Mail: akshay.bhamidipati@vanderbilt.edu

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### Introduction

Approximately 17 million people suffer from first-time strokes annually worldwide [1]. Beyond new strokes, there are over 80 million living people worldwide who have experienced a stroke. This results in approximately 116 million years of healthy lives that are lost to either death or disability in stroke survivors. Reports vary in exact figures, but approximately 23% to 75% of

stroke survivors suffer from fatigue [2]. Post-stroke fatigue (PSF) varies in definition, but is generally considered a chronic sense of difficulty conducting voluntary effort. It can occur independently of comorbidities and not surprisingly, treatments for comorbidities have shown little to no improvement in the main fatigue symptoms [3].

While treatments often provide little benefit to patients, PSF lowers quality of life and poses greater risks for death and other health conditions [2]. Herein, we aim to discuss post-stroke fatigue, its

prevalence, and several current methods used in its treatment.

### Stroke

Stroke is the second leading cause of death worldwide (behind ischaemic heart disease and ahead of COPD) and the third leading cause of disability worldwide [4, 1]. Every two seconds, someone in the world has a stroke [1]. This is not, however, limited to adults. In the UK alone, there are 400 childhood strokes [1]. Additionally, there are approximately 1.1 million new strokes in people under the age of 44 every year [5]. Moreover, racism and social determinism are considered risk factors implicated in stroke and post stroke symptoms. African Americans are twice as likely to have a stroke compared to Caucasians [1]. In addition, South Asians are more likely to have a stroke at a young age compared to white people [1]. After having a stroke, patients often suffer from disabilities, with rates of post-stroke disability almost 66% in the UK [1]. As such, understanding stroke and post-stroke disabilities is relevant to nearly every age group, as well as heavily related to ensuring equitable and fair healthcare worldwide.

### Ischemic Versus Hemorrhagic Strokes

Stroke is a common term used for a neurological insult that occurs due to poor oxygenation of brain tissue. The mechanism by which stroke occurs usually involves either ischemia from the vaso-occlusion of vessels supplying the nervous tissue or hemorrhage [6]. Cerebral circulation arises from the anastomosis of the internal carotids and the vertebral arteries. Ischemic stroke is caused by the occlusion of these vessels due to thrombotic or embolic events. In thrombotic events, the vaso-occlusion is caused due to the disease of the blood vessels like atherosclerotic disease [7]. In embolic events, stroke occlusion of the blood vessels supplying the brain occurs due to the mobilization of thrombosis from a cardiac or other arterial source [8].

The other major cause of strokes is hemorrhagic stroke. These events are usually caused by the rupture of blood vessels and bleeding into the brain. They can be traumatic, or, more commonly, have hypertensive etiologies. One can further subclassify hemorrhagic stroke based on the location of the bleed - intracerebral hemorrhage (bleeding into the parenchyma of the brain) and subarachnoid hemorrhage (bleeding into the subarachnoid space) [9]. Although there are two main types of stroke, including hemorrhagic and ischemic, ischemic is more common and is responsible for 87% of all stroke cases [10]. Hypertension is a major risk factor for both ischemic and hemorrhagic stroke. It has been reported in around two-thirds of every non-traumatic incident of stroke [11].

In ischemic stroke, the decreased blood flow causes hypoxia and necrosis of the brain tissue, ultimately leading into the loss of neuronal function [12]. Hemorrhagic strokes account for approximately 13% of all strokes but have a high mortality rate [10]. Hemodynamic changes (like increased pressure) cause blood vessels to rupture either in the intercranial space (causing an ICH) or in the subarachnoid space (causing an SDH). This can cause injury via the mechanism described above, but primarily, injury via hemorrhagic stroke is caused by an increase in intracranial pressure due to the mass effect of the hematoma [13].

### Stroke Symptoms

The early recognition of stroke is key in survival and rapid interventions can mitigate long-term sequelae. The American Stroke Association has suggested the acronym “ACT FAST” (drooping Face/uneven smile, Arm numbness and weakness, Speech Difficulty, and Time, i.e. early management) to help

recognize early symptoms of stroke. There are many consequences of cerebrovascular lesions. Depression is one of the most common and it affects around 40% of patients [14]. Decline in cognitive abilities is also reported [15].

In studying ischemic stroke, many investigations have identified key pathways that may contribute to accidental cell death, including ATP reduction and glutamate excitotoxicity. When nutrient supply to the brain is blocked, levels of brain glucose and oxygen are greatly reduced, preventing oxidative phosphorylation, the brain's main supply of ATP, from continuing. More specifically, deprivation of key nutrients triggers excess release of glutamate, leading to over activation of NMDA receptors and after a host of downstream effects, various forms of cell death [16]. However, the mechanisms of action of post-stroke symptoms are not well understood and are an area of active research [15].

Stroke is a major cause of disability worldwide, causing more types of disability than any other condition [1]. This can include both physical and emotional conditions such as difficulty speaking, visual problems, limb weakness, and imbalance. Fatigue is one such post-stroke symptom that is reported by many patients but is not well characterized by research. There appears to be no formal consensus on the definition or management of post-stroke fatigue [17]. In this review, we hope to elucidate what the scientific community means by post-stroke fatigue and the current management strategies used to combat it.

### Post-Stroke Fatigue (PSF)

As mentioned earlier, PSF is generally considered to be a sense of life-long fatigue occurring in stroke survivors. Though it affects numerous people and is ranked among the top ten research priorities for life after stroke, there are no effective treatments and little is known about its etiology [2]. Further, fatigue is the most common complaint from stroke-surviving patients and is generally the major factor restricting their lifestyle after strokes [18].

### Clinical characteristics of Post-Stroke Fatigue

Post-stroke fatigue affects patients in not only physical ways, but also mentally, emotionally, and socially. As such, it reaches into numerous aspects of their lives and treatments will require a nuanced understanding of each of the ways patients are impacted by the condition [19].

PSF results in poor quality of life, even when accounting for comorbidities such as depression, disability, and elderly age [20]. 40% of patients additionally cite it as their worst symptom of post-stroke recovery, as it gets in the way of everyday life such as eating, driving, reading, sleeping, and social activities [20]. Additionally, it causes patients to increasingly depend on their support structures, with some patients requiring institutionalization [20]. PSF has even been linked to increased mortality.

There are generally two kinds of post-stroke fatigue: exertion fatigue and chronic fatigue. Exertion fatigue generally occurs after intense physical or mental exertion. It occurs in the early stages after a stroke with a rapid onset and both quick duration and recovery [21]. On the other hand, chronic fatigue occurs in the later stages of post-stroke recovery and is characterized more by a general lack of interest or lack of motivation to conduct activities. Patients can have both exertion and chronic fatigue simultaneously, however exertion fatigue is more common after stroke and chronic fatigue is more common in patients with comorbidities such as multiple sclerosis [21].

## Defining Post-Stroke Fatigue and its Prevalence

In measuring the level of PSF a patient faces, studies have developed different fatigue scales; however, only a handful have been tested to show their validity with assessing PSF. Examples of scales include the Fatigue Severity Scale (FSS), the Fatigue Assessment Scale, the Checklist of Individual Strength, the Fatigue Impact Scale, and the Multidimensional Fatigue Inventory (MFI) [20]. Rather than using cut-off values in scales, it is now considered the standard to ask patients to self report whether they face fatigue significant enough to interfere with daily life [2]. This has been held up to be accurate and reliable in further studies.

However, there is still significant variability between studies in measuring the prevalence of post-stroke fatigue. This may be due to differences in the sample subjects of each study, how fatigue is assessed, when fatigue was assessed, cerebral location of the stroke, and other related factors, though it is not entirely clear. Small sample size is likely not the main factor. For example, in studies with greater than two hundred participants, fatigue levels have ranged from approximately 25% in some populations to 70% in others [20]. A report by Cumming et al. noted that between these two studies, one mitigating factor could be the exclusion of patients with PSF-related conditions [20]. For example, the study with 25% PSF rate excluded patients who also had depression. As depression and PSF are often found in patients together, this could be a significant reason as to why the prevalence of PSF was far lower in that study [20]. Similarly, time of assessment is a major factor in assessing PSF. Previous studies have shown that PSF has an onset within the first two weeks after a stroke, however the rate of PSF may decrease over time, suggesting that earlier assessments will result in greater prevalences of PSF in a sample [20]. This is of active discussion as some studies report increased prevalence of PSF over time, whereas other studies report decreased prevalence [20]. Surprisingly, even when these three factors are accounted for (differing scales, depression exclusion, and PSF diagnosis timing), there are still significant differences in PSF prevalence [20].

Of note, fatigue has been found to have significantly lower prevalence in Asian populations [20]. Explanations may include the younger age and increased likelihood of hemorrhagic stroke in these populations, however evidence does not readily support these ideas [20]. Thus, it is important to further investigate prevalence of PSF and develop more robust methods for diagnosing it among different people.

## PSF Treatments

With such high levels of stroke and PSF prevalence, as well as the significant degree to which PSF affects patients, developing adequate treatments is of paramount importance. To understand the best possible treatments, PSF is usually understood in terms of three categories: predisposing factors, triggers, and perpetuating factors [21]. Predisposing factors include “pre-stroke fatigue or pre-stroke depression”; triggers include “brain lesions, stroke-related inflammatory and neuroendocrine changes”; and perpetuating factors include “affective disorders, residual neurological deficits, cognitive decline, passive coping, reduced physical activity, locus of control, and self-efficacy” [21].

Related to predisposing factors, numerous patients with PSF suffer from sleep apnea and other sleep-related problems. However, addressing these sleep issues (such as improving sleep-related breathing issues) generally does not improve PSF patients’ fatigue [21]. Some work, though, has shown that increased physical

activity can lead to improved sleep quality for PSF patients. Additionally, treating pain may allow PSF patients to participate in exercise and thus improve pain-related mood and potentially sleep [21].

In addressing trigger factors, Modafinil has been found to significantly improve fatigue in PSF patients and improve quality of life without significant side effects [21, 22]. Modafinil is a neuroendocrine regulator and promotes wakefulness. Though this trial showed positive results, it only looked at patients in their third or later month of post-stroke symptoms. At these timepoints, many patients have passed the most acute stages of PSF. To better demonstrate and understand the efficacy of Modafinil, randomized controlled trials will need to be conducted. It would also be prudent to compare PSF to other fatigue patients, as well as looking at PSF at different timepoints after the initial stroke as suggested by Wu et al. [2].

Tackling affective disorders, antidepressants that are usually prescribed to address post-stroke depression are usually not significantly effective in improving fatigue in patients with PSF [21]. However, when patients present with PSF and depression, certain antidepressants or counseling may be effective in tackling the mental parts of fatigue. This can be understood in terms of PSF being a multifactorial, complex symptom following strokes [2]. Even in these cases though, gastrointestinal and CNS side effects sometimes occurred [21].

In treating psychological and behavioral aspects of PSF, it has previously been suggested that education for patients on topics such as sleep hygiene, nutrition, and relaxation can help treat fatigue in patients with PSF [21]. Similarly, cognitive behavioral therapy alongside graded physical activity training has also shown to reduce fatigue in PSF patients more than cognitive therapy alone [21]. Home versus hospital environments also play a role in patient recovery. For example, one study found that patients walked and stood more while at home than while in the hospital, even with a one week difference in time [21]. Thus, home environments may aid recovery. Additionally, many patients have found hospital environments to result in worse sleep, generally increasing fatigue [21].

## Discussion

Millions of people experience a stroke for the first time every year globally. Of these, anywhere from one quarter to three quarters (or even more) may experience post-stroke fatigue. This condition is highly debilitating, affecting nearly every aspect of patients’ lives. This includes social, mental, physical, emotional areas of their lives and can result in other health conditions, social isolation, and in some cases, even increased risk of mortality.

Currently, most post-stroke fatigue treatments are limited in their efficacy. Attempts have been made in breaking PSF down into components of predisposing factors, triggers, and perpetuating factors. Understanding PSF in this way allows for treatment of the condition from various angles to treat the specific symptoms and related factors. However, even this has yielded modest results at best. As of yet, pharmacological, physical, psychological, and environmental treatments have been suggested but none have been significantly successful in aiding patients at scale [23]. Truly tackling the condition will require a nuanced understanding of the condition’s etiology, an area which is now receiving more research endeavors.

Several ideas in this domain include the notion that stroke triggers biochemical imbalances leading to altered homeostasis which cause the symptoms of chronic PSF [24]. It is not yet clear which specific biochemical imbalances are markers for PSF versus its related comorbidities such as depression.

Furthermore, the few studies that have shown PSF as a potential result of biochemical imbalances studied markers in plasma [24]. This is potentially not reflective of PSF resulting from biochemical changes in the brain. De Doncker et al. have additionally suggested that studying cerebrospinal fluid markers for PSF can lead to more accurate PSF-specific markers and triggers. A 2019 study by Klinedinst et al. further found that platelet oxygen consumption rates (OCR) were negatively associated with fatigue at low levels of fatigue, potentially suggesting that low aerobic ATP generation could be a limiting factor in patient energy [19]. Further studies with larger sample sizes will be needed to confirm these findings and to identify the precise mechanisms by how this may be occurring.

#### Author Notes

\* These authors contributed equally to this publication

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