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The Biological Substrates of Poststroke Fatigue: a Qualitative Meta-Analysis for the Pathogenesis and Treatment of Poststroke Fatigue

Dr. Yasser Aladdin

[1]King Abdulaziz Medical City, Jeddah, Saudi Arabia
[2]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[3]King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
E-mail : yaladdin@ymail.com

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ABSTRACT

Stroke is the leading cause of physical disability worldwide and represents a black hole that drains the global health economy. Pathological post-stroke fatigue (PSF) is one of the most common sequelae, affecting up to 85% of stroke patients. Intractable PSF is the worst or one of the worst stroke symptoms in 40% of stroke survivors due to the overwhelming perceptual shortage of energy for physical and mental activities. The pathogenesis of PSF is blurred by a vast array of comorbidities inherent to this group of patients, which can precipitate fatigue regardless of the cerebrovascular injury. Fatigue is a subjective experience that may elude the quantification of uniform metrics. Quantitative meta-analysis on PSF studies is enigmatic due to the inconsistent study designs, methodology of fatigue assessment, and heterogeneity of patient characteristics.

This thematic meta-analysis scrutinizes the evidence for factors involved in PSF pathogenesis and constructs a clinical framework to approach PSF. Moreover, a treatment paradigm is proposed based on the compound evidence-weighted extractions of data from prospective studies on PSF. Moreover, proactive testing for autonomic reflexes and postural hypotension is of paramount importance, and judicious selection and titration of antihypertensives may correct subclinical orthostatism that manifests seamlessly as morbidly chronic fatigue. PSF may hinder rehabilitation and impact morbidity and mortality. Embracing the proposed treatment paradigm and tracing the pathogenic factors will minimize morbidity and redeem the global economy layers and years of additional costs in stroke care.

Methods: Qualitative Meta-analysis.

Keywords: Poststroke Fatigue.

1. Introduction

According to WHO, stroke was defined as rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin[1]. According to Global Health Data Exchange, stroke was the second largest cause of death globally (5.5 million deaths) after ischemic heart disease in 2016. Stroke is one of the leading global causes of mortality and major disabilities with a wide spectrum of physical, mental, and social derangments[2]. Post-stroke fatigue (PSF) is an ''overwhelming feeling of exhaustion or tiredness'' unrelated to exertion and does not typically improve with rest[3-4].

Fatigue is one of the most common symptoms after stroke with reported rates between 25 and 85% depending on study design, time point, and methods of assessment[5-6]. The considerable variation in the rates of stroke-related fatigue reflects the common confounding comorbidities that can potentially precipitate fatigue independent of cerebrovascular injury. Many confounding comorbidities either coexist or represent the long-term sequelae of previous cerebral infarcts. Depression, obesity, obstructive sleep apnea, low physical activity, and vascular cognitive impairment are a few examples.

The objective of this thematic analysis is to criticize the available evidence for the potential etiologies of PSF because intractable PSF may drain resources, impact the quality of life, hinder poststroke rehabilitation, prolong morbidity, and is associated with increased mortality. PSF features an overwhelming lack of endurance with a perceptual shortage of energy for routine physical and mental activities. However, PSF is defined by set scores on fatigue scales used in other chronic fatigue disorders, which are not specific for stroke populations[7].

2. Materials and Methods

Search Strategy: A systematic search of the MEDLINE database was performed via PubMed (up to November 2024) using combinations of the keywords "fatigue" and "poststroke fatigue" with "stroke." Time and language limitations were not applied.

Eligibility Criteria: Only clinical trials, randomized clinical trials, and original observational studies of patients with stroke and fatigue were included. Interventional trials or treatment studies were included if the findings probe potential biological etiologies for PSF. The studies had to assess PSF using a fatigue scale or a case definition with a valid analysis for putative associations between PSF and other factors. Studies lacking primary data, including traditional medicinal practices, editorials, reviews, case studies, or protocol papers were excluded. Systematic reviews, meta-analyses, and association studies were included in the appraisal process under specific associated factors. Quantitative meta-analysis was not performed due to the heterogeneity of populations, different study designs, and inconsistent methodology of fatigue assessment.

3. Natural History of Poststroke Fatigue

The symptomatology of PSF represents a constellation of objective and subjective experiences in a significant proportion of ischemic stroke patients, approaching 50% in some cohorts. Fatigue is a complex multidimensional percept of impaired endurance to exertion that interferes with the rehabilitation of stroke survivors. Fatigue was originally considered a symptom of post-stroke depression. However, cumulative evidence showed that fatigue occurs in patients without depression which resulted in the definition of a "post-stroke fatigue syndrome". Fatigue is a complex entity with objective and subjective manifestations, whereas objective symptoms are the observable decrement in performance during the repetition of physical or mental tasks. Subjective aspects represent the frustrating internal weariness and aversion to physical and mental efforts. Fatigue can temporally be divided into early (up to 3 months post-stroke) and late fatigue (over 3 months post-stroke), with early

fatigue always associated with late fatigue[7]. About five assessment studies evaluated the natural history of PSF and captured three distinct patterns for the temporal expression of PSF, including persistent fatigue, recovered fatigue, and late-onset fatigue[7-12].

More than one-third of patients developed fatigue during the acute period within the first 3 months after the indexed stroke. Two-thirds of patients with fatigue continue to have fatigue in the late stage, defined as one year after the stroke, representing the persistent fatigue group. One-third had experienced recovery and represented the recovered fatigue group. About 12-58% of patients without fatigue during the initial assessment developed fatigue during a later stage, representing the late-onset fatigue group.

A recent systematic review on the time course of PSF showed the prevalence of PSF was 42% at six months after ischemic stroke and 34% at one year. Sixty-six percent of patients with PSF on initial assessment remained fatigued at follow-up, and of those without initial PSF, 15% developed PSF at follow-up[13]. The magnitude and quality of symptoms vary greatly, and the linear increment may suggest that PSF may emerge with the increment in physical and mental activities during recovery.

4. Significance of Poststroke Fatigue

4.1 IMPACT OF POSTSTROKE FATIGUE

5. Fatigue was described as the worst or one of the worst symptoms by 40% of stroke survivors and contributed to functional impairment up to 13 months after stroke[14]. A study of 96 patients to evaluate acute phase fatigue and later outcomes found that acute phase fatigue was an independent risk factor for poor long-term physical outcomes after 18 months of follow-up[15]. The effect of acute phase fatigue was reflected in the physical outcome, but not mental status after controlling for relevant covariates. However, neither physical nor mental status during the acute phase predicted fatigue at 18 months, and the best predictor for fatigue after 18 months was acute phase fatigue. The findings of acute phase fatigue are corroborated by prior studies showing that PSF is likely to persist over time. A study on more than a hundred patients showed that baseline fatigue did predict fatigue outcomes over time and early interventions might prevent the progression of PSF[10]. Predictors for early fatigue were younger age, post-stroke depressive symptoms, and infratentorial infarctions.

Moreover, PSF is also associated with higher morbidity and may entail a higher fatality. Two separate studies have shown that PSF, either within 6 months or 2 years after stroke, predicts death in the following year after controlling background variables[16-17]. Fatigue is also found to be an independent predictor for institutionalization and dependency of activities of daily living functions[16]. Three years after the stroke, patients with fatigue also had a higher case fatality rate. This cumulative evidence may indicate that early and late-onset PSF conceivably share a common pathophysiological substrate. Cox regression analysis in another study of 377 patients showed that PSF is associated with higher mortality[17]. In another study of 190 patients, both fatigue and depression are associated with long-term mortality in young adults with ischemic stroke, irrespective of stroke severity[18]. Fatigue was also associated with reduced long-term survival in a study of 1080 patients randomized in the International Stroke Trial at a mean of 64 weeks after stroke onset[19]. It is unlikely that PSF directly increases mortality, but PSF is linked to other factors associated with raised mortality, namely diabetes mellitus and myocardial infarction[17-18].

4.2 DEMOGRAPHIC FACTORS

Multiple studies have documented an increased prevalence of PSF in female patients[16,17,20-22]. Increasing age was also found to have a higher risk for PSF[14,20,23]. One study from New Zealand on 612 patients with PSF showed the only baseline variables independently associated with increased risk of PSF were pre-stroke incontinence and being of European ethnicity[23]. The association between PSF and social factors, marital status, educational

level, family income, or educational level was not consistently and unequivocally established[24]. PSF was associated with more significant disability, dependency, and failure to return to work in multiple studies[12,17,27,28]. In a linear regression model, the Hamilton Depression Rating Scale, pre-stroke fatigue, and the National Institutes of Health Stroke Scale score at admission were significant correlates of the Fatigue Severity Scale, accounting for 36% of the variance of it[28]. Thus, PSF has a specific pattern of impact on patients' everyday lives. Additionally, patients with PSF were found to have higher odds of developing post-stroke pain[29].

5. Etiology of Poststroke Fatigue

The pathophysiological mechanism of fatigue is not precisely understood, and deciphering the mechanism is further challenged by the association of PSF with independent intrinsic and extrinsic variables. The heterogeneity of studies in design, methodology, time frames, and population characteristics hinders systematic interpretation and extrapolation of unequivocal causality. The essence of fatigue symptomatology is partly a subjective phenomenon that intricately relates to multiple variables at an individualized level. Factors will be mentioned in accordance with available evidence. A visual scheme for the factors involved in PSF is summarized in Figure 1.

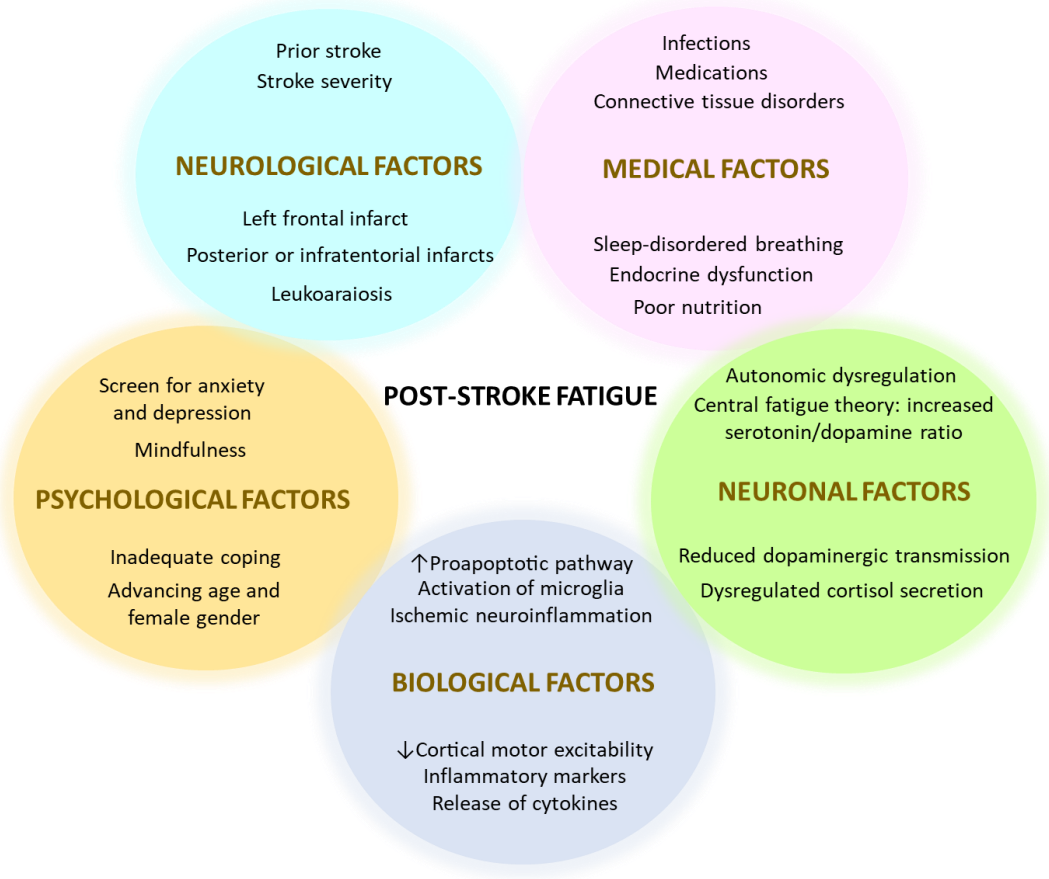

Figure 1: Visual summary of the multifactorial pathogenesis of post-stroke fatigue

5.1. PSYCHOLOGICAL FACTORS

Logistic regression analysis of 377 patients reveals that PSF is independently associated with pre-stroke depression, leukoaraiosis, myocardial infarction, diabetes mellitus, pain, and sleeping disturbances[17]. Emotional function and mental health along with female gender and advancing age were associated with increased fatigue rates at 64 weeks after stroke onset[19]. The link between fatigue and mortality is broader, including a

connection to diabetes mellitus, myocardial infarction, and psychosocial factors[18]. Concomitance of depression and fatigue has been a long-recognized relation in patients with ischemic stroke[25]. Forty-five studies have found a correlation between PSF and poststroke depression[24]. Fatigue has been long addressed as one facet of major depressive disorder and as a frequent symptom in patients with depression and other psychiatric disorders[25]. In one prospective study of 260 patients, the domains of retardation and interest/fatigue on Hamilton Depression Rating Scale carried the highest odds risk factor for developing major depression after stroke[26]. Patients with post-stroke depression were slower and more fatigued than non-depressed patients, which may impact extended rehabilitation. Forty-five studies have found a correlation between PSF and poststroke depression[24].

Poststroke depression has been reported between less than 25% and more than 75%[30]. While the role of the side and site of the infarct remains controversial, depression may preferentially develop after an anteriorly situated stroke in the left hemisphere[31]. Poststroke depression is a significant factor in functional disability, even long after neurological and neuropsychological recovery[26]. Fatigue is commonly present in depression and constitutes one of the criteria for depression in most scales[30,32]. However, fatigue is not a mere element of poststroke depression and can occur in the absence of depressive mood, a dissociation which is better remarked in Parkinson's disease and multiple sclerosis (MS)[33,34].

Another study of 155 patients aimed to assess affective changes in patients with unilateral stroke of less than 55 years of age and with no history of prior psychiatric disturbances. Twenty subjects were finally assessed using the Hamilton Depression Rating Scale. Four patterns of affective response to stroke were identified and included (1) no affective symptoms, (2) verbal distress only, (3) vegetative symptoms only, and (4) a combined disorder with both distress and vegetative symptoms. The presence of verbal distress, vegetative signs, or both was associated with extended hospital stays and more significant neuropsychological impairment. The authors suggested that emotional distress was due to a psychological reaction to the stroke, while the vegetative symptoms resulted from the organic damage[35].

Fatigue, emotional lability, impaired memory, and concentration difficulties were found frequent in survivors of stroke and myocardial infarctions without association with cognitive or neurological deficits. Therefore, a psychological stress response syndrome due to inadequate coping was suggested as one mechanism of PSF[36]. One prospective cohort of 99 patients aimed to explore the relation between PSF and poststroke mood, cognitive dysfunction, disability, and infarct site to assess the predictive factors in the development of PSF following minor infarcts. The three most powerful correlates of PSF at 6 months were initial stroke severity, disability, and depression. The most powerful correlates for PSF at 1 year were depression, anxiety, and language deficit. Attentional-executive impairment, depression, and anxiety levels remained associated with PSF throughout this period, underlining the critical role of these variables in the genesis of PSF[12]. These findings suggest that the stroke itself may be one determinant trigger of early PSF rather than late fatigue, with psychological factors necessary for both early and persistent PSF[7].

5.2. NEUROLOGICAL FACTORS

Fatigue is an integral component in the symptom profile of multiple neurological disorders, most notably in multiple sclerosis, Parkinson's disease, chronic inflammatory polyradiculoneuropathy, postpolio syndrome, autonomic failure, and amyotrophic lateral sclerosis. The coexistence of these disorders conceivably increases the odds of developing PSF. Different neurological factors may influence the development of PSF at various time points after stroke. In one study, infratentorial stroke was associated with fatigue at 2 months but not 18 months after stroke; however, baseline depression and anxiety were associated with

fatigue at both assessments[10]. Fatigue was even recorded after TIA with lower mean fatigue scores than in patients with minor cerebral infarction[17]. Ischemic and hemorrhagic strokes have about the same impact on fatigue in multiple studies[9,11,14,16,20,22,27,37]. In one study of 107 patients with ischemic or hemorrhagic stroke, features on post-stroke CT do not appear to be associated with fatigue at 1 month. However, clinically diagnosed posterior strokes along with female gender, anxiety, and depression were linked to the rates of PSF. Therefore, clinical vigilance rather than isolated CT features may predict fatigue early after stroke[38]. Previous stroke was also significantly associated with an increased risk of PSF[16,23,39,40].

The evidence for the relation between stroke severity and fatigue was mixed and the association was not significant when poststroke depression was excluded in studies that showed such association. One study compared PSF after TIA versus minor stroke, and the prevalence of fatigue after minor stroke was higher than after TIA, suggesting that PSF is not absolutely due to the cerebral event, disability, comorbidity, medications, or other confounders[41]. The findings indicate that PSF in patients without neurological impairment has a central origin rather than increased physical efforts to overcome stroke.

The mainstream literature does not provide a discrete relation between the stroke side or site and the development of PSF. However, infratentorial strokes, posterior stroke, and basilar infarct were associated with PSF in some series[10,38,42]. Further differentiation of infarct location revealed that patients with cortical infarcts had higher scores for cognitive fatigue, while subcortical infarcts correlated with higher scores for physical fatigue[43]. Based on supportive neuropathological data, it was proposed that central fatigue is due to a failure to integrate limbic input and motor functions in basal ganglia with disruption of the striatal–thalamic–frontal cortical system[44].

In line with the hypothesis of subcortical frontal injury, imaging studies of PSF revealed that infarcts in basal ganglia, particularly the caudate and putamen were independent predictors for the development of PSF[45,46]. Logistic regression showed that PSF was independently associated with leucoaraiosis, and white matter hyperintensities were shown as independent predictors for persistent PSF in non-depressed patients one year after the indexed stroke[17,47].

5.3. MEDICAL FACTORS

Fatigue is frequently encountered in patients with inflammatory, cancer, endocrinological, infectious, and connective tissue disorders[25]. It may also develop without any antecedent condition other than a viral infection, leading to what is known as chronic fatigue syndrome[25]. A host of comorbidities interrelated to stroke may produce fatigue syndrome, including obstructive sleep apnea and systemic inflammatory disorders such as giant cell arteritis or systemic lupus erythematosus with or without vasculitis. Stroke patients with comorbid cancer undergoing chemotherapeutic treatment or with HIV have conceivable etiology for developing fatigue or worsening of coexisting PSF. One study of stroke survivors six months after the event revealed the bidirectional relation between fatigue and poor nutritional status. Thus, persons with fatigue are more prone to poor nutritional status, and those with poor nutritional status are at greater risk of nutritionally related fatigue[48]. Common comorbid conditions such as hypertension on long-term antihypertensive may develop hypotension if their medications are not adjusted and accordingly may worsen the ongoing fatigue syndrome.

Another plausible factor for PSF is the frequent rates of sleep disturbances after stroke. Sleep architecture is disturbed in stroke patients regardless of the presence of sleep-disordered breathing (SDB). Stroke patients have reduced total sleep time and efficiency with reduced slow-wave sleep, increased wakefulness, and prolonged sleep latency. Rapid eye movement (REM) sleep is reduced when SDB is also present[49]. Other polysomnographic sleep studies in stroke patients have reported both increased insomnia with

difficulty initiating and or maintaining night sleep and hypersomnia with excessive daytime sleepiness[50]. Conversely, pain after stroke was commonly associated with PSF in multiple studies[16,17,29,47,51]. Analyses of the triad of poststroke pain, poststroke depression, and PSF showed that two or three symptoms were logistically associated with a high modified Rankin Score, prior stroke, prior diabetes mellitus, and prior depression. PSF was commonly related to poststroke pain and poststroke depression in contrast to the low association between depression and pain in patients without PSF[51]. The associations are dynamic and reflect distinct symptom clustering in stroke patients, particularly as the severity of symptoms increases with the number of co-occurring symptoms. The association of stroke with diabetes mellitus, hypertension, dyslipidemia, and cardiac disorders is established, and each entity can potentially precipitate fatigue directly or by the medications used in each condition. Dissecting potential culprits for fatigue in stroke patients remains at the discretion and the skills of the treating physician. Multiple medications have been found to precipitate fatigue, including sedatives, antidepressants, and antihypertensive drugs[28,51,52,53].

5.4. BIOLOGICAL FACTORS

5.4.1. Neurophysiology

Fatigue is classified as physical or mental, and physical fatigue can be classified as peripheral or central (spinal or supraspinal). During physical fatigue, the peripheral sensory system activates an inhibition system to limit motor output from the primary motor cortex (M1) (supraspinal fatigue) while motivational input activates a facilitation system to increase M1 output to overcome supraspinal fatigue. Hence, the balance between inhibition and facilitation systems determines primary motor cortex output. The fatigue model in neurological disorders suggested that suppression of excitatory rather than overactivity of inhibitory systems may underlie fatigue[54]. Patients with PSF have impaired cortical excitability by transcranial magnetic stimulation (TMS) on minimally impaired stroke survivors with PSF. Reduced corticospinal excitability is one possible mechanism underlying fatigue as fatigue scores correlated positively with higher TMS thresholds. Fatigue is perceived when volitional inputs to the motor cortex produce less than expected output due to reduced excitability. The overall cortical motor excitability, both the motor outputs and the inputs that drive motor output, are diminished in PSF. Moreover, central activation failure is more significant in patients with high 'perception of efforts', a secondary measure of fatigue, i.e., patients who perceive a task to be more effortful exhibit more central activation failure[54]. Neuronal excitability partly depends on spontaneous neuronal firing rates, and reduced neuronal firing after stroke will impair neuronal excitability[56].

5.4.2. Ischemic Neuroinflammation

Fatigue frequently coexists with systemic inflammatory disorders and infections. Activation of inflammatory cascades results in the secretion of immune signaling mediators such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α), and all have corresponding CNS receptors[57]. Ischemic stroke results in microglia activation at the infarct region with subsequent release of cytokines and cytotoxic free radicals[58]. Moreover, activation of proapoptotic pathways occurs by early upregulation of Toll-like receptors in neurons and neighboring microglia and astrocytes. This mounting immune response will cascade in the propagation of inflammatory responses and eventual neuroglial injury[59]. The cytokine IL-6 is involved in fatigue development in autoimmune and non-autoimmune disorders and is associated with higher fatigue scores. It is secreted during acute and chronic inflammatory responses by many cells, including immune, endothelial, and muscle cells[60]. Interleukin-6 levels correlated with infarct volume, white blood cell count, and acute phase C-reactive protein[61]. Alternatively, other contradicting results also exist where the levels of cytokines were similar in fatigued and non-fatigued MS patients, including levels of interleukin-35, interleukin-2, interleukin-1β, and TNF-α[62].

5.5. NEURONAL FACTORS

5.5.1 Central Fatigue

The contribution of the brain to exercise-induced fatigue is termed central fatigue. Regular exercise has been shown to enhance dopaminergic transmission with upregulation of tyrosine hydroxylase mRNA expression, reduced D2 autoreceptor mRNA in substantia nigra pars compacta (SNpc), and increased D2 postsynaptic receptor mRNA in the caudate and putamen, the primary projection site of SNpc[63]. The result is translated in that habitual exercise enhances dopamine synthesis, reduces D2 autoreceptor-mediated inhibition of dopaminergic neurons in SNpc, and increases D2 receptor-mediated inhibition of the basal ganglia. Impaired dopaminergic transmission could account for the central fatigue in PSF patients. The original central fatigue hypothesis suggests that exercise-induced increase of serotonin in certain brain regions induces fatigue[64]. Serotonin is linked to fatigue because of its effects on sleep, drowsiness, and loss of motivation. Nonetheless, central energy reserves rely not on a single neurotransmitter but on complex interactions between dopaminergic, serotonergic, and catecholaminergic neurotransmission. The revised central fatigue theory dictates that an increase in the central ratio of serotonin to dopamine is associated with feelings of tiredness and lethargy[64]. The role of dopamine in central fatigue is pronounced in the studies of physiological responses to amphetamines. In contrast, the role of norepinephrine and serotonin is reflected in exercise during heat as noradrenergic and serotonergic projections innervate the thermoregulatory centers of the hypothalamus. We may hypothesize that physical interruption of catecholaminergic outflow to the hypothalamus or dopaminergic projections to basal ganglia by ischemic infarcts or subsequent immune responses could account for PSF.

In addition, the brain-derived neurotrophic factor (BDNF) is an essential neurotrophin for synaptogenesis and synaptic plasticity in normal conditions and after neuronal injury. Dopaminergic neurons express BDNF with its receptor TrkB, and both are upregulated within CNS by voluntary exercise, leading to delayed onset of fatigue[63,65]. Mental fatigue with psychomotor slowing and memory disturbances, particularly in the hippocampal region, relies on its availability. Conversely, inflammatory cytokines promote excitotoxic injury to glutamatergic neurons, causing neuronal and glial cell injury, which breaks down the blood-brain barrier and impairs homeostasis and metabolism[66]. Reduced cerebral glucose metabolism in the frontal cortex and basal ganglia was evidenced in one study using 18F-deoxyglucose PET scan in patients with MS-related fatigue[67]. Brain glucose hypometabolism correlated positively with the Fatigue Severity Scale; however, depression could not be ruled out as a potential etiology of cerebral hypometabolism as depression is not addressed in the fatigue questionnaire. Functional MRI studies during motor tasks in fatigued MS patients to investigate the functional correlates of central fatigue revealed reduced activation of the left middle temporal gyrus, left supplementary motor area (SMA), bilateral superior frontal gyrus, left postcentral gyrus, and basal ganglia[68]. Fatigued patients displayed increased activation of the right middle frontal gyrus with reduced recruitment of the right thalamus and SMA, and these changes were correlated with fatigue scores. Abnormal patterns with impaired activation timing between motor areas and cortical neural networks may contribute to central fatigue.

5.5.2. Endocrine dysfunction

The hypothalamic-pituitary-adrenal axis (HPA) controls the release of glucocorticoids, while the central autonomic nervous system releases catecholamine. The activity of both systems is modulated by stress, diurnal variation, and cytokines, as interleukin receptors are widespread in the HPA axis and afferent vagal ganglia[69]. Initial hyperactivity of the HPA axis occurs in the acute phase of stress, including stroke. However, with continuous stimulation, a blunting response results

in decreased diurnal cortisol secretion and reduced glucocorticoid production, culminating in fatigue and depression[70]. Cortisol has negative feedback on the sympathetic system and cytokine production, which diverts immune responses towards the humeral side [66,69]. Reduced corticotrophin production and impaired HPA axis were noted in chronic fatigue syndrome and autoimmune conditions[71]. However, further studies are required in PSF because contradicting data also showed similar HPA hormonal levels in fatigued and non-fatigued MS patients[62].

5.5.3 Autonomic dysregulation

Orthostatic intolerance due to neutrally-mediated syncope or orthostatic tachycardia was noted in patients with chronic fatigue syndrome[72]. Another study revealed systemic hypertension above 145/90 mmHg and low daytime diastolic blood pressure (BP) drop below 50 mmHg on 24-hr ambulatory BP monitoring in patients with PSF[53]. However, it remains to be determined if the dysregulated BP, the side effects of antihypertensive drugs, or other comorbidities such as depression could have contributed to fatigue. Another recent model of central fatigue was proposed by Hanken et al. in patients with MS in which proinflammatory cytokines activate vagal afferents which convey the signals to interoceptive brain areas, such as the nucleus tractus solitaries, hypothalamus, insular cortex, anterior cingulate cortex, and amygdala[73]. These interoceptive brain regions integrate visceral sensory information and regulate autonomic outflow[74]. Activation of vagal afferent with subsequent activation of vagal efferents results in chronic parasympathetic overactivity with disruption of normal autonomic tone[75]. Cognitive fatigue and autonomic dysfunction were shown in one study to have a strong correlation between the fatigue scale and the COMPASS-31 autonomic scale, which corroborates the model that fatigue may partly result from an inflammation-induced increase in vagus nerve activity[74]. The imbalance between sympathetic and parasympathetic tone may disrupt the dynamic real-time autonomic machinery, conceivably creating physical and mental fatigue. The author's unpublished research of detailed autonomic testing in patients with PSF showed features of partial autonomic failure and sympathoadrenergic deficit manifesting as a recurrent orthostatic drop in BP in patients with PSF.

6. Fatigue Measurement

Various measures of fatigue have been implemented in the studies on PSF, and the lack of standardized objective measures may have resulted in a wide variation in reported rates of PSF. Among over 50 fatigue scales used in research, only seven were tested for their psychometric properties in a stroke population. All showed feasibility and validity in assessing PSF, but none met all the criteria for psychometric robustness and clinical utility. The most comprehensive and psychometrically vigorous measures were the Neurological Fatigue Indices[7,76]. Of the 52 scales identified, the SF-36v2 (vitality component), the fatigue subscale of the Profile of Mood States, the Fatigue Assessment Scale, the general subscale of the Multidimensional Fatigue Symptom Inventory, and the Brief Fatigue Inventory had the best face validity. All scales were valid and feasible for stroke patients, but the Fatigue Assessment Scale had the best test-retest reliability despite the poorest internal consistency[77].

Dichotomizing patients by a single cut-off score may not fully identify pathological fatigue in stroke survivors[14,25]. To address this weakness, a case definition for PSF was developed with self-reported significant fatigue that interfered with daily activities. A case definition with face validity and structured interview was constructed to ensure feasibility, test-retest and interrater reliability, and concurrent validity about four fatigue scales [20]. The probe questions demonstrated feasibility for test-retest reliability. Patients fulfilling the case definition also had substantially higher fatigue scores on four fatigue severity scales, indicating concurrent validity. Nevertheless, judicious use of scales and meticulous screening will likely identify a sizable portion of stroke survivors with a degree

of fatigue at the physical or mental spectrum. Early identification will guide management, including fastidious evaluation of comorbidities, medications, and other stroke complications.

7. Treatment

The ultrastructural mechanisms for the perceptual lack of energy are still not precisely defined in PSF. The current symptomatic therapy reflects the lack of a specific biological substrate. A summary of the relevant randomized clinical trials of relevance to the pathogenesis of PSF is summarized in Table 1. Based on this review of the available evidence, a proposed scheme for the treatment paradigm of PSF is outlined in Figure 2. Most pharmacotherapies implement either wakeful-promoting agents or antidepressants[78,79]. Modafinil, a neuroendocrine regulator and wakefulness-promoting agent, stimulates the monoaminergic pathways and shows neuroprotective properties. Modafinil significantly reduced post-stroke fatigue and improved quality of life without significant adverse events[78]. However, this trial recruited patients ≥3 months after the stroke and not in the more acute phase of PSF. The response to modafinil was remarkable in patients with brain-stem or thalamic strokes but not in patients with cortical infarcts. A study implementing resting-state functional MRI data and independent component analysis was used to extract functional networks. Resting-state functional connectivity between baseline, modafinil, and placebo treatment was examined using permutation testing with threshold-free cluster enhancement. Modafinil treatment increased functional connectivity in the right hippocampus with lower connectivity in the left frontoparietal, primary somatosensory cortex, and mesolimbic network in the temporal pole. Modafinil induced significant changes in functional connectivity, which conceivably relate to the reduction of PSF. However, the relationship between sensory processing, neurotransmitter expression, and fatigue requires further exploration[80].

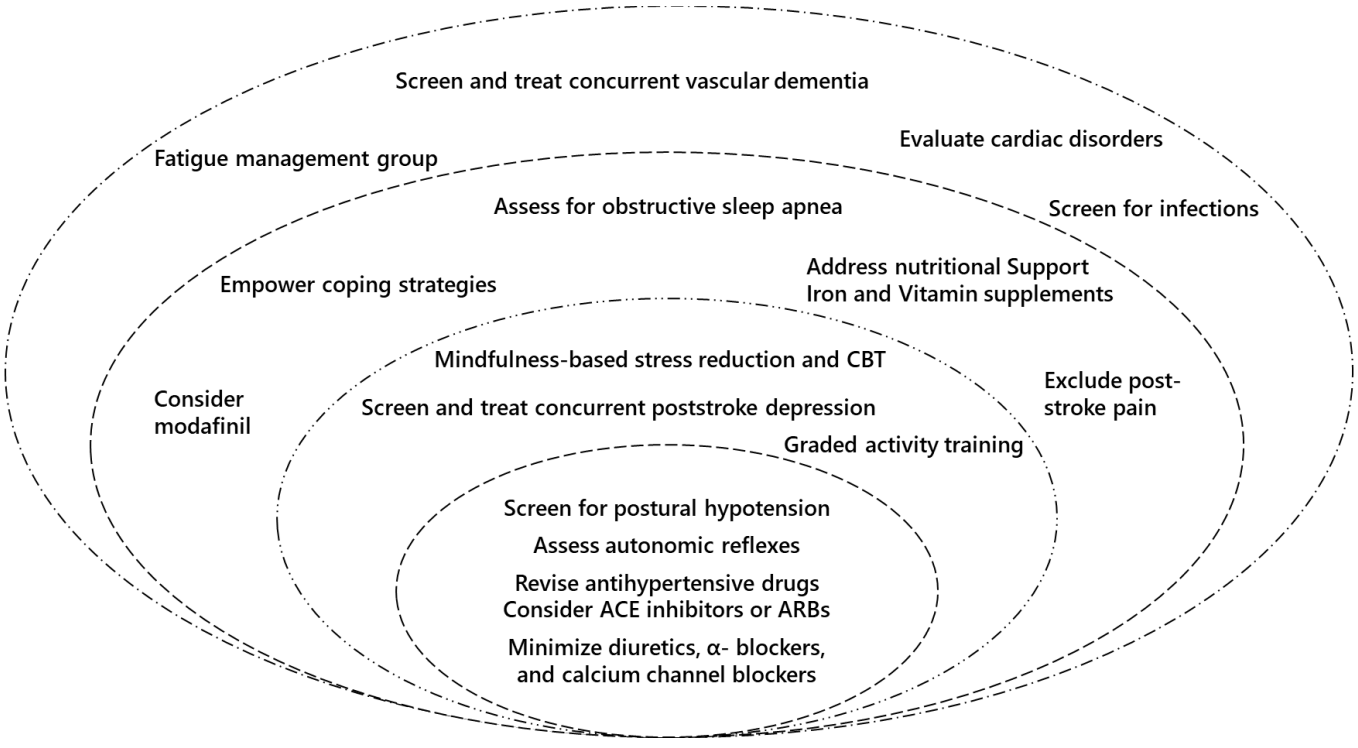

Figure 2: Proposed treatment paradigm for post-stroke fatigue based on the compound weight of evidence. *ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin-II receptor blockers; CBT: cognitive behavioral therapy.*

Table-1: Key clinical trials and randomized clinical trials of relevance to the etiopathogenesis of post-stroke fatigue

Authors	*Year*	*Patients*	*Study Title*
Giovannini S et al.	2024	24	The role of nutritional supplement on post-stroke fatigue: a pilot randomized controlled trial
Nilsson MKL et al.	2020	30	Effect of the monoaminergic stabiliser (-)-OSU6162 on mental fatigue following stroke or traumatic brain injury
Blomgren C et al.	2019	296	Long-term performance of instrumental activities of daily living in young and middle-aged stroke survivors-Impact of cognitive dysfunction, emotional problems and fatigue
Visser MM et al.	2019	26	Predicting Modafinil-Treatment Response in Poststroke Fatigue Using Brain Morphometry and Functional Connectivity
Nguyen S et al.	2019	15	Cognitive behavioural therapy for post-stroke fatigue and sleep disturbance: a pilot randomised controlled trial with blind assessment
Karaiskos D et al.	2012	60	Duloxetine versus citalopram and sertraline in the treatment of poststroke depression, anxiety, and fatigue
Zedlitz AM et al.	2012	83	Cognitive and graded activity training can alleviate persistent fatigue after stroke: a randomized, controlled trial
Clarke A et al.	2012	19	Poststroke fatigue: does group education make a difference? A randomized pilot trial
Johansson B et al.	2012	32	Mindfulness-based stress reduction (MBSR) improves long-term mental fatigue after stroke or traumatic brain injury
Mead GE et al.	2011	1080	Fatigue after stroke: baseline predictors and influence on survival. Analysis of data from UK patients recruited in the International Stroke Trial
Jaracz K et al.	2007	50	Clinical and psychological correlates of poststroke fatigue. Preliminary results
Choi-Kwon S et al.	2007	83	Fluoxetine is not effective in the treatment of post-stroke fatigue: a double-blind, placebo-controlled study

A Continuous Positive Airway Pressure (CPAP) trial in patients with PSF was ineffective unless the patients had symptomatic sleep apnea syndrome[81]. Interventions to treat suspected sleep apnea with CPAP have been frequently attempted in patients with PSF. However, CPAP is not practical in relieving PSF unless accompanied by symptomatic sleep apnea syndrome. Overall, studies on treatment modalities for PSF are also limited, and a Cochrane review concluded that there is insufficient evidence to support any pharmacological or nonpharmacological intervention for the treatment of PSF[82,83]. Antidepressants for poststroke depression, such as fluoxetine, citalopram, duloxetine, and sertraline, have not been shown to improve PSF[79,83,84]. Therefore, depression and fatigue are conceivably two distinct domains of poststroke complications, even if the antidepressant effect may address the mental aspects of fatigue[83,85]. Moreover, poststroke pain may need to be routinely screened in patients with PSF as poststroke pain has been correlated to PSF in seven studies[16,17,29,47,51,86,87]. The association between poststroke pain and PSF is inconsistent in other studies, but 10% of patients displayed the triad of fatigue, depression, and pain, and 20% experienced fatigue and pain without depression[24]. Conversely, one conceptual

model for PSF provides a multidisciplinary approach to address predisposing factors, triggers, and perpetuating factors[88]. The model may guide the dissection of relevant factors and develop individualized treatment strategies.

Non-pharmacological modalities to target cognitive behavioral therapy, graded exercise, and adaptive pacing therapy have been effective in other fatigue disorders[89]. A pilot study showed that a group education program, sleep hygiene, relaxation exercise, physical exercise, nutrition, and mood significantly improved PSF symptoms[83,90-93]. A novel, non-pharmacological strategy tested treatment with mindfulness-based stress reduction over 8 weeks and showed promising results on a self-assessment scale for mental fatigue and neuropsychological tests. Despite the small sample size, significant improvements were achieved in the self-assessment and the neuropsychological tests, digit symbol-coding, and trail-making test[94]. Nutritional supplementation with sucrosomial iron and vitamin C in concert with intensive rehabilitation improved motor and cognitive performance in a small study[95]. Supplementation with the monoaminergic stabilizer (−)-OSU6162 showed substantial improvements in mental fatigue in a subgroup of patients. The tolerability and observed therapeutic effects of this compound are promising in treating the mental fatigue symptomatology of PSF[96]. One facet to address PSF is that fatigue, cognitive dysfunction, and post-stroke depression negatively impacted instrumental activities of daily living in stroke survivors even seven years after the stroke[97]. Cognitive dysfunction and depressive symptoms can be found even among stroke survivors with mild or no remaining neurological deficits.

The orthostatic drop in PSF reflects functional disturbances to central autonomic networks, resulting in partial sympathetic failure with impaired cardiovagal compensatory responses. Autonomic impairment may explain the increased mortality in the strata of stroke with PSF and may project fatigue as a red flag for autonomic assessment in patients with stroke. Clinicians should be cautious about iatrogenic factors impeding autonomic responses, particularly the selection and dosing of antihypertensive drugs. Orthostatic changes in BP and HR should be assessed in stroke clinics for patients with undue physical or cognitive fatigue. Treating PSF begins by discrete monitoring for the side effects of each drug or drug combination. Prudent selection and titration of antihypertensives may correct subclinical orthostatism that manifests as morbid PSF in selected patients.

Parasympathetic cardiovagal responses and baroreflex sensitivity are also reduced proportionally to the greater demands of orthostatic intolerance in patients with PSF. Addressing autonomic responses introduces a new treatment paradigm to address plausible biological substrates for PSF. Minimizing direct vasodilators and diuretics will conceivably improve the impaired baroreflex in PSF. Alternatively, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists provide attractive choices that will not challenge the counterregulatory reservoir of baroreflex in PSF. Sympathetic vasoconstrictor drugs might also be avoided in patients with PSF for the generic risk of hypertensive crisis in patients with impaired baroreflex. Beta-blockers can be continued, particularly in the presence of ischemic heart disease. Overall, these details aim to reduce the associated mortality of PSF and enhance the chances for meaningful recovery in stroke survivors.

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Have No Conflict of Interest to Disclose.

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