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LITERATURE REVIEW

POST-STROKE FATIGUE: PREVALENCE, PREDISPOSING FACTORS, AND MANAGEMENT STRATEGIES

(*POST-STROKE FATIGUE: PREVALENSI, FAKTOR PREDISPOSISI, DAN STRATEGI PENATALAKSANAAN*)

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ABSTRACT

Post-stroke fatigue (PSF) is a common and challenging condition that affects 42% to 53% of stroke survivors. It is characterized by persistent exhaustion that does not improve with rest and can significantly affect rehabilitation, daily activities, and overall quality of life. While the exact causes of PSF are not fully understood, various biological and physiological predisposing factors play a role in its onset. Biological factors include age, gender, stroke characteristics, and inflammatory responses, while physiological factors involve comorbidities, pre-stroke fatigue, and sleep disturbances. Psychological aspects, particularly depression and anxiety, are also closely linked to PSF, though their causative role is still debated. Diagnosis relies on subjective assessments, such as fatigue questionnaires, and objective measures, including electromyography (EMG) and electroencephalography (EEG). Management strategies include both pharmacological and non-pharmacological approaches. Dopamine reuptake inhibitors, such as modafinil, have shown potential benefits, whereas selective serotonin reuptake inhibitors, such as fluoxetine, have not demonstrated significant effects. Non-pharmacological approaches offer promising results in fatigue management, including physical exercise, cognitive behavioral therapy, psychoeducation, and transcranial direct current stimulation (tDCS). Given the multifactorial etiology of post-stroke fatigue, a multidisciplinary management strategy is essential. Optimizing recovery requires personalized interventions that combine pharmacological and non-pharmacological therapies tailored to the individual's specific clinical profile.

Keywords: post-stroke fatigue, rehabilitation, stroke

ABSTRAK

Post-Stroke Fatigue (PSF) adalah kondisi umum yang memengaruhi 42% hingga 53% penyintas stroke. Kondisi ini ditandai dengan kelelahan persisten yang tidak membaik dengan istirahat, sehingga secara signifikan menghambat rehabilitasi, fungsi sehari-hari, dan kualitas hidup secara keseluruhan. Mekanisme PSF masih belum sepenuhnya dipahami, tetapi berbagai

faktor predisposisi (biologis, fisiologis dan psikologis) berkontribusi terhadap perkembangannya. Faktor biologis meliputi usia, jenis kelamin, karakteristik stroke, dan respons inflamasi, sedangkan faktor fisiologis mencakup komorbiditas, kelelahan sebelum stroke, dan gangguan tidur. Faktor psikologis, terutama depresi dan kecemasan, juga memiliki hubungan erat dengan PSF, meskipun masih diperdebatkan. Diagnosis PSF bergantung padapenilaian subjektif, seperti kuesioner kelelahan, serta peniliaian objektif seperti elektromiografi (EMG) dan elektroensefalografi (EEG). Strategi penanganan melibatkan pendekatan farmakologis dan non-farmakologis. Inhibitor reuptake dopamin, seperti modafinil, telah menunjukkan manfaat potensial, sedangkan inhibitor reuptake serotonin, seperti fluoxetine, belum menunjukkan efek yang signifikan. Pendekatan non-farmakologis, termasuk latihan fisik, terapi perilaku kognitif, psikoedukasi, dan stimulasi arus searah transkranial (tDCS), memberikan hasil yang menjanjikan dalam manajemen kelelahan. Berdasarkan etiologi multifaktorial dari kelelahan pasca-stroke, suatu strategi tatalaksana multidisiplin menjadi suatu keharusan. Optimalisasi pemulihan memerlukan intervensi yang dipersonalisasi melalui kombinasi terapi farmakologis dan non-farmakologis yang disesuaikan dengan profil klinis spesifik individu.

Kata kunci: post stroke fatigue, rehabilitasi, stroke

INTRODUCTION

Fatigue is a subjective experience that ranges from mild tiredness to extreme exhaustion and can affect both healthy individuals and those with medical conditions. Normal fatigue, which occurs after extended physical exertion or long work hours, typically subsides with rest or sleep. In contrast, chronic fatigue persists despite rest and is often associated with underlying health conditions such as stroke, multiple sclerosis, and cancer.[1]

Post-stroke fatigue (PSF) is a frequent and challenging symptom that can affect stroke survivors of any age or gender, even those who appear to have completely regained their functional abilities. The prevalence of PSF has been reported to range from 42% to 53%.[1,2] Variations in prevalence across studies may reflect differences in study populations, stroke onset, and the assessment methods used.[3] Numerous studies have examined the factors that contribute to PSF, producing varying results. Despite its widespread occurrence, PSF is often overlooked in clinical settings, which may result in poor rehabilitation outcomes, reduced quality of life, delayed return to work, and even higher mortality rates.[2]

Given its significant impact on stroke recovery, a better understanding of PSF is essential. This review aims to provide a comprehensive overview of PSF, including its definition, classification, predisposing factors, consequences, and available management strategies.

DISCUSSION

Fatigue

Fatigue is a complex and multifactorial condition that can

significantly affect an individual's physical, cognitive, and psychological well-being. Fatigue may arise from two primary pathways: central fatigue, which involves the central nervous system (CNS), and peripheral fatigue, which primarily affects the muscles. Central fatigue is characterized by a decline in voluntary muscle activation and is associated with reduced motor neuron firing frequency, impaired synchronization, and weakened cortical motor signals. In contrast, peripheral fatigue is characterized by reduced muscle contractile strength and disruptions in action potential transmission within muscle fibers.[4,5]. Fatigue impairs physical and cognitive performance but typically resolves with rest in healthy individuals. However, in pathological conditions such as chronic fatigue syndrome, multiple sclerosis, and stroke, fatigue persists despite adequate recovery. The progressive decline in motor function due to fatigue impairs daily activities and overall quality of life.[4,6]

Fatigue is a multifaceted phenomenon that cannot be easily compartmentalized into entirely distinct "central" or "peripheral" mechanisms. Current scientific literature suggests these classifications are theoretical constructs that limit a comprehensive understanding of fatigue. The governor theory proposes that fatigue arises from the interaction of homeostatic, physiological, and psychological factors, regulated by a negative feedback system that adjusts bodily functions dynamically. Physiological and metabolic changes occur in response to external fluctuations rather than being confined to a single system. These external influences shape behavioral patterns, which are driven by voluntary adjustments rather than fixed sensory inputs. Therefore, fatigue is an integrative process involving multiple physiological and psychological systems rather than a localized dysfunction, highlighting its complexity in both medical and performance contexts.[4]

Central Fatigue

Central fatigue is defined as the inability to initiate and maintain voluntary motor activity due to dysfunction of the central nervous system (CNS). It is primarily influenced by biochemical alterations in neurotransmitters such as serotonin, dopamine, glutamate, and gamma-aminobutyric acid (GABA). Elevated extracellular serotonin levels during extended physical exertion are linked to sensations of lethargy and diminished motor drive. The ratio of serotonin to dopamine is essential in controlling motivation and arousal, influencing the onset of fatigue. A

reduction in dopamine release from the substantia nigra pars compacta (SNPC) decreases basal ganglia activation, resulting in reduced cortical stimulation and the development of fatigue. While elevated dopamine levels during physical activity are initially beneficial, they eventually become self-limiting, contributing to central fatigue. Glutamate, the primary excitatory neurotransmitter, plays a vital role in regulating motor cortex activity. Impairments in glutamate transporter 1 (GLT-1) and excitatory amino acid transporters (EAATs) interfere with glutamate clearance, leading to excitotoxicity and fatigue. Furthermore, increased GABAergic activity reduces motor neuron excitability, limiting voluntary muscle activation and contributing to fatigue.[4]

In central fatigue, neural drive from the primary motor cortex to the neuromuscular junction, is reduced, The strength of this neural signal determines the force that a muscle can generate. Even with maximal effort, voluntary activation remains below its peak, meaning the neuromuscular system cannot achieve the muscle's full potential force. As exertion persists, voluntary activation continues to decline, demonstrating the progression of central fatigue. During maximal effort, this reduction is associated with increased motoneuron pool inhibition, which may alter reflex input from type III and IV muscle afferents (spinal mechanisms), and diminished supraspinal drive from the motor cortex. In submaximal efforts, supraspinal fatigue becomes more dominant, resulting in task failure due to inadequate descending motor drive. This underscores the involvement of both cortical and spinal mechanisms in controlling voluntary activation, ultimately influencing muscle endurance and performance in both maximal and submaximal conditions.[7]

Several brain regions help maintain internal stability during activity by adjusting vascular resistance to ensure sufficient blood flow. Areas such as the vestibular nuclei, cerebellar vermis, and flocculus contribute to balance and coordination, while the medulla and pons regulate respiratory and cardiovascular function. Impaired cerebral perfusion or physiological stress reduces functional activity in visual-processing regions (dorsal occipital cortex, superior colliculi, and lateral geniculate body), signaling compromised homeostasis. The CNS responds by reducing motor output and increasing perceived effort, which are core features of central fatigue. The insular cortex plays a key role in this process by integrating internal body signals; its right hemisphere is associated with sympathetic nervous activity, while the left supports

parasympathetic regulation. An imbalance between these systems may further enhance the perception of fatigue and limit physical performance.[4,8]

Peripheral Fatigue

Peripheral fatigue results from biochemical and metabolic disturbances within the muscle fibers, leading to impaired force generation and muscle contraction. Key contributing factors include the accumulation of metabolic byproducts, disrupted ion homeostasis, and failure of excitation-contraction coupling. High levels of reactive oxygen species (ROS), inorganic phosphate (Pi), hydrogen ions (H+), and lactic acid disrupt muscle contractility and ATP resynthesis.[4] Increased extracellular potassium (K+) impairs muscle excitability, thereby reducing contraction efficiency.[4] Impaired calcium (Ca^{2+}) release and uptake within the sarcoplasmic reticulum decrease actin-myosin interaction, leading to diminished contractile force.[4] Three primary mechanisms drive peripheral fatigue: (1) energy metabolism failure, (2) reduced cross-bridge cycling efficiency, and (3) metabolic acidosis.[4]

Central and peripheral fatigue are separate yet interrelated processes that both contribute to the overall experience of fatigue. This phenomenon is particularly relevant in individuals with neurological disorders such as stroke. In 1983, Leegaard reported that many stroke survivors experienced widespread brain-related symptoms, including fatigue and difficulty concentrating. Up to 75% of these patients reported fatigue as their most frequent symptom.[2]

Post Stroke Fatigue

Stroke complications often include fatigue.[9] Fatigue is understood as a subjective experience, with its perception being affected by multiple contributing factors.[4] Post-stroke fatigue (PSF) is a complex condition that greatly influences recovery after a stroke, impacting physical, cognitive, and psychological functions.[10,11] The etiology of PSF remains unclear, but several biological, physiological, and psychological factors have been identified as contributing to its development (Figure 1).[2]

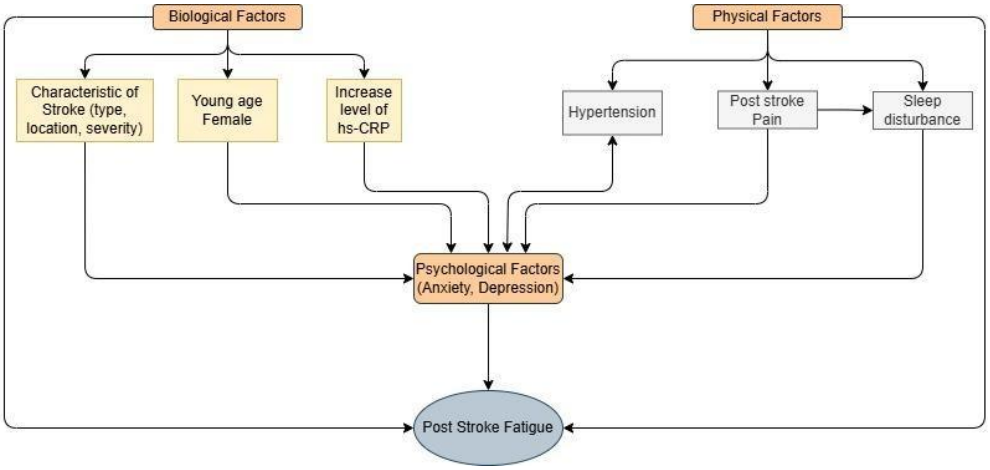

Figure 1 Connection between predisposing factors and mechanism of PSF development.[2]

Predisposing Factors of PSF

Biological Factors

Age and sex have been considered potential risk factors for PSF; however, research findings remain inconsistent. Some studies suggest that older patients may be less susceptible to PSF during the subacute and chronic phases, while others report a higher occurrence among elderly patients. Likewise, the role of sex remains uncertain, with some studies indicating a higher prevalence in females, possibly due to hormonal and psychosocial factors.[2] Identifying the influence of demographic factors on PSF prevalence remains challenging, as fatigue is generally more common among older adults and women.[12]

Stroke characteristics, such as lesion location and severity, may also contribute to PSF. Fatigue has been linked to infarcts in certain brain areas, including the basal ganglia, corona radiata, and internal capsule, within the first three months after a stroke. Additionally, infarcts in the caudate and putamen have been associated with PSF, especially during the subacute phase. Furthermore, patients with mild ischemic stroke have been reported to experience greater fatigue compared to those with transient ischemic attack (TIA).[2,13] Variations in the prevalence of PSF have been observed between ischemic and hemorrhagic stroke patients, with reported rates of 36% and 66%, respectively.[9]

Inflammation is a significant biological factor in PSF. Elevated levels of high-sensitivity c-reactive protein (hs-CRP) and interleukin-1β (IL-1β) have been associated with PSF for up to six months following a stroke.[2,14] Persistent inflammatory responses may lead to neurotransmitter imbalances, particularly involving serotonin, dopamine, and norepinephrine systems, thereby contributing to PSF pathophysiology.[2,14]

Physiological Factors

Many stroke patients have coexisting comorbidities, such as heart failure, kidney disease, diabetes mellitus, and hypertension, each of which may independently contribute to fatigue.[13] Hypertension and diabetes mellitus have been linked to PSF during the chronic phase. Furthermore, fatigue experienced before the stroke has been recognized as a predictor of PSF onset, particularly within the first two weeks post-stroke. Sleep disturbances, which affect up to 78% of stroke patients, also represent a significant factor in the development of PSF.[2,13] Additionally, post-stroke pain impairs function and is more strongly associated with fatigue than depression, with chronic pain sustaining long-term fatigue over time.[13]

Psychological Factor

Psychological distress, including depression and anxiety, is strongly associated with PSF.[4] Fatigue may increase the risk of developing depression and can also occur as one of its symptoms.[15] Depression is a key predictor of PSF during both the acute and chronic phases, affecting motivation, activity levels, and mental fatigue. The influence of depression on post-stroke fatigue may vary according to stroke severity. Stroke severity and neurological impairments appear to contribute more substantially to early exertional fatigue, whereas depression becomes more influential during later stages of recovery.[13] Anxiety has been more closely linked to physical fatigue than cognitive or emotional aspects. The relationship between psychological disorders and PSF remains bidirectional,[2] patients. This assessment tool is applicable across different demographic groups, including age and sex. Objective assessments include the six-minute walk test (6MWT), electromyography (EMG), and electroencephalography (EEG). The latter provides insights into neuromuscular fatigue and changes in brain activity associated with this condition.[2,16]

Impact of PSF

The impact of PSF extends to quality of life, rehabilitation outcomes, and long-term functional independence. Patients with persistent fatigue demonstrate increased dependence in activities of daily living (ADLs) and are less likely to return to work. Furthermore, PSF is an independent predictor of post-stroke mortality.[17,18] Studies indicate that fatigue raising questions about causality. However, factors such as personal difficulties, anxiety, reduced arousal levels, and decreased physical capacity have been linked to distinct patterns of brain activation and the development of

CNS fatigue.[4]

Assessment of PSF

The assessment of fatigue following stroke involves both subjective and objective measures. The Fatigue Severity Scale (FSS) is the commonly used subjective assessment tool, while the Neurological Fatigue Index-Stroke (NFI-Stroke) is specifically validated for stroke in stroke patients may be associated with increased mortality rates and impaired functional recovery. In addition, research has identified fatigue as a strong predictor of suicidal ideation, regardless of the presence of depressive symptoms.[19]

Management Strategies of PSF

At present, no standardized treatment exists for PSF due to its multifaceted etiology.[20] Pharmacological interventions, such as modafinil, have shown potential in alleviating PSF symptoms, whereas fluoxetine has not demonstrated significant benefits.[21,22] Likewise, another study found that citalopram, sertraline, and duloxetine were ineffective in reducing PSF, though duloxetine was the most effective agent in relieving anxiety.[13]

Modafinil is a wakefulness-promoting agent and central nervous system stimulant that primarily acts by stimulating monoaminergic pathways, resulting in elevated levels of neurotransmitters such as histamine, norepinephrine, serotonin, dopamine, and orexin. It may also exert neuroprotective effects by enhancing antioxidant activity and reducing oxidative stress in neurons. By increasing the availability of cortical neurotransmitters, modafinil may support neural repair and recovery. Its low potential for drug interactions and generally mild side-effect profile make it a promising treatment option, particularly for older adults. Reported side effects include headache, nausea, insomnia, and nervousness.[21,22]

In a randomized controlled trial involving individuals with chronic stroke, a 6-week course of modafinil at a dose of 200 mg/day resulted in a significant reduction in self-reported PSF compared with placebo. Although the underlying neurophysiological mechanisms of PSF are not fully elucidated, emerging evidence from neuroimaging and electrophysiological studies implicates a striato-thalamo-frontal motor facilitation circuit. This pathway is thought to enhance primary motor cortex output, thereby compensating for fatigue and preserving motor performance.[21,22]

Disruption of this facilitatory network may contribute to the pathogenesis of PSF. In particular, deficits in motor facilitation may explain the reduced physical endurance and decreased motor cortex excitability frequently

observed in stroke survivors.[21,22]

Non-pharmacological interventions, including psychoeducation, physical exercise, and neuromodulation techniques such as transcranial direct current stimulation (tDCS), have shown promise in addressing post-stroke symptoms. Transcranial direct current stimulation is a non-invasive brain stimulation technique that modulates cortical excitability by delivering a low-intensity (1–2 mA) direct current through scalp electrodes. It typically uses an anodal and a cathodal electrode to complete the circuit. Anodal stimulation enhances cortical excitability, while cathodal stimulation produces an inhibitory effect. Targeted stimulation of the motor cortex using tDCS has been shown to not only affect the localized area but also modulate activity in adjacent regions, altering functional connectivity across neural networks. Notably, combined stimulation of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) significantly increases M1 excitability for at least 30 minutes post-intervention. Advantages of tDCS include its cost-effectiveness, portability, ease of administration, and good tolerability. Reported side effects are generally limited to mild tingling sensations at the electrode sites.[23,24]

Transcranial direct current stimulation (tDCS) has been shown to modulate both neurotransmitter dynamics and cortical excitability, resulting in transient improvements in PSF. Emerging evidence suggests that tDCS significantly elevates dopamine and serotonin concentrations in the frontal cortex, while concurrently reducing GABAergic activity and increasing intracellular calcium (Ca^{2+}) levels. These neurochemical changes are thought to enhance motor function and alleviate fatigue symptoms. Collectively, these findings underscore the potential of tDCS as an adjunctive therapy for PSF, particularly when integrated with conventional rehabilitation strategies.[24,25]

Regular exercise improves mitochondrial function, reduces inflammation, and balances neurotransmitters, thus alleviating fatigue. In parallel, cognitive behavioral therapy (CBT) has demonstrated efficacy in alleviating PSF. By addressing maladaptive behavioral patterns and cognitive distortions, CBT offers a structured, individualized approach to symptom management and relapse prevention.[23]

The complex nature of post-stroke fatigue means that no single treatment is universally effective. While some medications, such as modafinil, have shown promise, others have not demonstrated similar benefits, highlighting that PSF has multiple causes

requiring different solutions. This evidence points to the need for a combined strategy that requires a multifactorial approach addressing physical, neurological, and psychological factors.

Therefore, a multidisciplinary approach is essential. Optimizing recovery requires personalized interventions that integrate treatments like brain stimulation, physical exercise, and cognitive therapy according to each patient's specific clinical needs and symptom profile. Future research should focus on identifying which patients will benefit most from specific combinations of these therapies.

CONCLUSION

Post-stroke fatigue (PSF) is defined as a persistent feeling of exhaustion that does not improve with rest and significantly affects daily functioning. Despite its high prevalence, the exact pathophysiology remains uncertain and is influenced by various factors. This condition negatively affects rehabilitation, physical activity, quality of life, and long-term recovery, leading to increased dependence in performing daily activities and a higher risk of mortality. To assess its severity, several evaluation tools are utilized, including the NFI-Stroke, 6MWT, EMG, and EEG.

Management includes pharmacological and non-pharmacological approaches that have been developed, with varying outcomes. Given its complex nature, a multidisciplinary approach is essential. Future research should focus on personalized interventions to optimize recovery.

CONFLICT OF INTEREST

This article was written without any conflicts of interest.

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