Poststroke Asthenic Disorder

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Abstract

Asthenic disorders are seen in approximately half of poststroke patients. The mechanisms underlying poststroke asthenia (PSA) are related to brain connectome damage, as well as neuroinflammatory and neuroendocrine mechanisms. PSA is associated with a lack of energy, lassitude, and fatigue that do not improve after rest or sleep; it is differentiated from depression, apathy, and daytime sleepiness. Risk factors for PSA include female gender, anxiety and depressive disorders, severe neurological deficit, sleep disorders, diabetes etc. Treatment of PSA includes cognitive behavioral therapy graded physical activity, and pharmacotherapy.

Keywords: *stroke; asthenia; fatigue; tiredness; depression*

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Астеническое расстройство после инсульта

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Аннотация

Астенические расстройства отмечаются примерно у половины пациентов после инсульта. Механизмы развития постинсультной астении (ПИА) связаны с поражением коннектома головного мозга, нейровоспалительными и нейроэндокринными механизмами. Для ПИА характерны нехватка энергии, вялость, быстрая утомляемость, которые не уменьшаются после отдыха или сна; её дифференцируют с депрессией, апатией и дневной сонливостью. Факторами риска по развитию ПИА являются женский пол, тревожно-депрессивные расстройства, выраженный неврологический дефицит, нарушения сна, сахарный диабет и др. В лечении ПИА используются методы когнитивно-поведенческой терапии, дозированные физические нагрузки, фармакотерапия.

Ключевые слова: *инсульт; астения; усталость; утомляемость; депрессия*

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Asthenic disorder is a condition manifested by increased tiredness with very unstable mood, reduced self-control, impatience, restlessness, disturbed sleep, loss of the ability for prolonged mental and physical effort, as well as intolerance to loud sounds, bright light, and strong odors [1]. Asthenic disorder is a major compo-

nent of neurasthenia (i.e. a form of neurotic disorder) and can be observed in patients with medical conditions or central nervous system (CNS) damage [1, 2]. The prevalence of asthenic disorder in the general population varies from 1.5% to 15% [1]. Asthenia is observed in half of patients with Parkinson's disease [3]; in patients with multiple sclerosis its prevalence can be up to 78% [4].

In Western scientific literature, authors traditionally use the more general term "fatigue", which reflects only the major manifestation of asthenia. This term implies pathological fatigue, which, unlike physiological fatigue, does not depend on previous physical activity and does not decrease after rest or sleep [5].

Asthenia (pathological fatigue) is a significant challenge to poststroke patients. According to experts, this phenomenon is one of the key areas for research when studying stroke sequelae [6]. Given that the terms "asthenia" and "pathological fatigue" are essentially the same, we will use the term "poststroke asthenia" (PSA) in this article. Currently there is no commonly accepted definition of PSA. Some authors define it as a state of subjective feeling of fatigue and exhaustion that develops regardless of previous stress and does not decrease after rest or sleep [7].

Epidemiology

PSA is observed in many patients; according to several authors, its prevalence can be up to 90% [7]. T. B. Cumming et al. conducted a systematic review of 22 studies that used the Fatigue Severity Scale (FSS) to assess PSA. The average prevalence of PSA was 50% (95% confidence interval [CI] 43–57%). In comparative analysis, fatigue prevalence was found to be lower in studies conducted in Asian countries (35%; 95% CI 20–50%) [8]. A meta-analysis conducted by I. Alghamdi et al. in 2021 included 35 studies (6851 patients) and yielded comparable results; PSA prevalence was 48% (95% CI 42–53%) and 48% (95% CI 43–53%) using FSS and Multi-dimensional Fatigue Inventory (MFI), respectively [9].

The prevalence of PSA remains high both in the acute period and several years after stroke. According to A. Pedersen et al., in 7 years post-stroke, up to 80% of the patients reported PSA symptoms [10].

Pathophysiological mechanisms

Currently, the mechanisms underlying asthenia in patients with neurological disorders are considered from the perspective of the set point theory. According to this theory, the body can function in an optimal way only while being in a state of balance between various multidirectional physiological processes. This is called a set point. Disturbed set point leads to asthenia. This is caused by various mechanisms [2]. They can be classified into neuroimmune, neuroendocrine, neurochemical, neurophysiological, etc. [11].

The pathogenesis of PSA is currently not well understood. A single experimental PSA study was conducted by A. Kunze et al. [12]. Its results showed significant differences in behavioral correlates of fatigue and depression in different rat strains for up to 50 days after experimental stroke. In particular, Sprague-Dawley (SD) and Wistar rats increased spontaneous activity during the light cycle, when the rodents are not active, and decreased spontaneous activity during the dark cycle, when they should be active, which is an equivalent of fatigue. Lewis rats had high spontaneous activity during the dark cycle but increased duration of immobilization in the forced swim test, which was consistent with the phenomenon of learned helplessness and considered to be an equivalent of depressive disorder in this species. Lewis rats also had significantly increased serum levels of interleukin-10 *vs*. SD and Wistar rats. The authors concluded that these changes were related to inter-strain differences in the development of the immune response, and PSA and depression were caused by different neuroimmune mechanisms related to poststroke aseptic inflammation [12]. Inflammation is associated with increased blood levels of cytokines and leads to neurochemical disturbances in the CNS due to inhibition of indoleamine 2,3-dioxygenase and switching of tryptophan metabolism from serotonin to kynurenine, a neurotoxic compound [13].

Neuroimmune mechanisms are likely to play the most significant role in the development of so called early-onset fatigue, which is seen during the first year after stroke [14]. W. de Doncker et al. provided information that cytokine and kynurenine blood levels were higher and tryptophan index (ratio of tryptophan to competing amino acids) was lower in patients with fatigue 12 months post-stroke. At 18 months post-stroke, this pattern was not seen [15].

Subsequently, the neuroimmunological theory of PSA was confirmed in molecular genetic studies, which showed that patients carrying C allele of interleukin-1 receptor antagonist gene were more prone to develop poststroke asthenia. On the other hand, TLR4 allele carrier status, which has anti-inflammatory properties, reduced the risk of PSA [16].

The neuroendocrine theory explains the development of PSA by the insufficiency of the endocrine glands and by metabolic disorders. According to different authors, the prevalence of poststroke pituitary dysfunction can be up to 82%. Somatotropic hormone insufficiency is the most common. Somatotropic hormone is produced in the lateral parts of the anterior pituitary, which

is most susceptible to damage during stroke. Data on the relationship between pituitary insufficiency and PSA are inconclusive. The role of neuroendocrine dysfunction in PSA is being investigated in the PIT-FAST study [17].

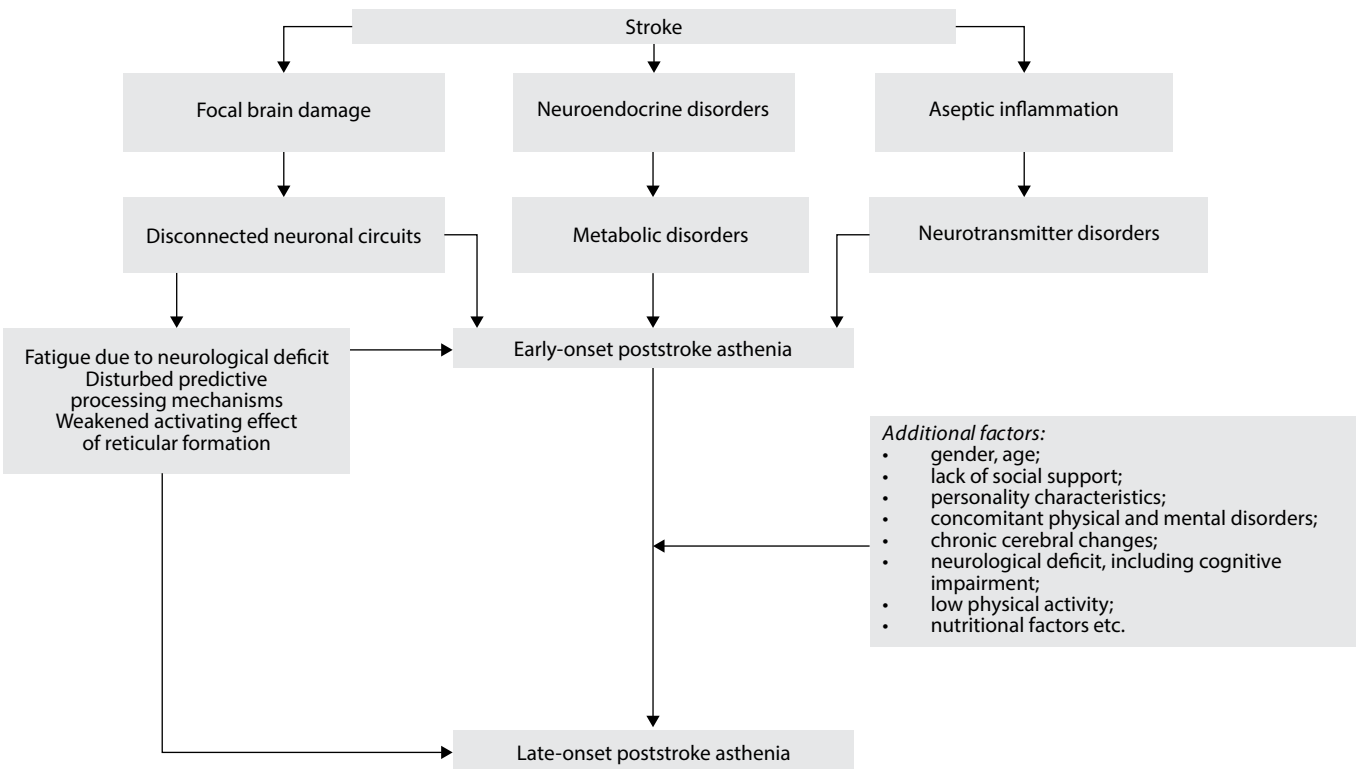
A study using brain magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) and resting-state functional mapping showed that disruptions in structural and functional connectivity play an important role in the development of PSA after middle cerebral artery stroke. The most important changes include connectivity disruptions in the ipsilesional rostral middle frontal cortex, with greater structural disconnection correlating with more severe asthenia [18].

Recently, several neurobiological theories explaining PSA development have been proposed. Motor activity is normally accompanied by the perception of effort required for muscle contraction. Perceived effort results from the integration of afferent input from muscles and sensory prediction. The sensory attenuation model explains the development of asthenia by increased perception of effort due to disturbed gate control mechanism of motor sensations [15].

The metacognitive dyshomeostasis model is related to predictive coding theory (predictive processing). According to this theory, the brain constantly creates and updates its internal model of the environment. It generates internal afferent input, which is then compared with the actual afferent input. If they do not match with each other, prediction errors are formed, which are then used to update the internal model. Many predicting errors make the brain to pay more attention to internal input, which in turn reduces the patients' self-confidence (i.e. self-efficacy), and this may underlie the development of asthenic disorders.

The inhibitory sensitization model explains the development of asthenia by the fact that excessive excitation of the activating systems of the brain increases the sensitivity of the inhibitory systems of the CNS. This leads to constant signaling from the brain about the need for rest, which makes the patient feel exhaustion and fatigue.

Considering the data presented, we can assume that different mechanisms may underlie early-onset and late-onset PSA. Biological mechanisms (e.g. neuroimmune, neuroendocrine, etc.) play a more significant role in the development of early-onset asthenia, while additional factors (e.g. age, comorbidity, etc.) lead to the chronic process and late-onset asthenia (Figure). The said theories can explain PSA only partially, so its mechanisms are still being investigated [15].



PSA pathogenesis model.

Factors associated with PSA

Group of factors	Factors
Demographic and socioeconomic	Female gender, low social support
Psychological/psychophysiological	Depression, anxiety, cognitive impairment, external locus of control, coping strategy (avoidance, confrontation), sleep disorders
Neurological	Severe neurological deficit (assessed by NIHSS, mRs), hemorrhagic stroke [20]
Laboratory	Decreased thyroid-stimulating hormone [22], increased uric acid [23], cytokines, neutrophil-lymphocyte ratio, decreased prognostic nutritional index [24], increased C-reactive protein [25]
Physical	Arterial hypertension and hypotension, type 2 diabetes, musculoskeletal pain, cardiac arrhythmia, obesity [26]
Neuroimaging	Strokes involving the thalamus, basal ganglia, or infratentorial structures; leukoaraiosis
Pharmacological	Statins, antidepressants, muscle relaxants, polypharmacy

Note. NIHSS, National Institutes of Health Stroke Scale; mRs, modified Rankin scale.

Data on the association between stroke lesion localization and PSA are of special interest. Damage to the brain stem and basal ganglia is thought to lead to asthenia due to damage to the ascending activating reticular formation and changes in the volitional sphere, respectively. However, a meta-analysis conducted by J. Shu et al. did not confirm any significant association between stroke location and PSA [20]. The stroke lesion itself and, therefore, partial disconnection of the brain connectome might be sufficient to significantly increase the likelihood of developing asthenic disorder. This hypothesis was confirmed by C. Winward et al., who showed that the prevalence of fatigue was higher after minor stroke than after transient ischemic attacks. In other words, transient symptoms were observed in both groups clinically but, in patients with stroke, an acute ischemia lesion was detected, which probably caused a higher prevalence of fatigue in this group [21].

Some factors may play a dual role in the development of PSA. For instance, obese patients were less likely to develop asthenia in the acute stage of stroke; however, they were more prone to fatigue 6 months post-stroke [26].

A systematic review of studies investigating the association between PSA and cognitive impairment gave inconclusive results. Four studies found significant correlations between PSA and memory, attention, speed of information processing, and reading speed (r from −0.36 to 0.46), whereas seven studies did not [27]. The role of speech disorders in PSA has not been established completely due to the fact that aphasia is a common exclusion criterion in many studies [28].

Low physical activity before and after stroke may predispose the patient to the development of asthenia. A systematic review by F. Duncan et al. did not show any evident association between fitness and PSA [29]; however, D. Tai et al. in their meta-analysis showed that physical exercise improved pathological fatigue in post-stroke patients [30].

It is especially important to define modifiable PSA risk factors, which may include chronic pain, increased anxiety, polypharmacy, uncontrolled medical conditions, and low level of physical activity. Managing these factors can be considered an approach to the prevention and treatment of PSA.

Socioeconomic factors play an important role in the development of stroke and its complications [31]. Low level of social support was shown to increase risk of PSA [7].

Considering the high prevalence of asthenia after COVID-19, we can assume that the risk of PSA development after COVID-19-related stroke might be increased [32]. However, this has not been studied yet.

Assessment of poststroke asthenia

Several scales are used to assess PSA. The most popular scale is the Fatigue Severity Scale (FSS), which consists of 9 items, with each item scored from 1 to 7. It allows differentiating PSA from depression; however, its sensitivity in evaluating pathological fatigue over time may be inadequate. The Fatigue Impact Scale (FIS) consists of 40 items, with each item scored from 0 to 4. The disadvantage of this psychometric tool is a relatively large number of items. The Modified Fatigue Impact Scale (mFIS) does not have this drawback and consists of 21 items. Its disadvantages include the fact that it is mainly aimed at assessing the impact of pathological fatigue on the patient's daily living. Other scales include Fatigue Assessment Scale and Vitality Subscale of the SF-36 scale. The simplest tool to assess PSA is a fatigue visual analogue scale. However, its validity is significantly lower than that of the above-mentioned scales [7]. When using the scales, the patient is diagnosed with PSA if their score is higher than a certain value. The scores can be also used to assess the severity of fatigue.

J. Lynch et al. proposed a case definition for pathological fatigue after stroke in inpatients and community patients. It also allows differentiating PSA from daytime sleepiness [5].

PSA case definition for community patients. The patient has felt fatigue, a lack of energy, and increased need to rest every day or nearly every day for at least 2 weeks in the past month. This fatigue has led to difficulty taking part in everyday activities.

PSA case definition for inpatients. Since their stroke, the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities (for inpatients this may include therapy and may include the need to terminate an activity early because of fatigue). If the patient's condition conforms to this definition, they can be diagnosed with PSA.

A comparative analysis of the above definitions showed that they assess more the impact of PSA on daily activities, while many scales rather reflect PSA symptoms. A disadvantage of the case definition is its inability to assess PSA severity and characteristics. PSA can be diagnosed using either the scales or case definition; however, more sensitive and specific PSA assessment tools are still being developed.

Differential diagnosis

Differential diagnosis of PSA includes clinically similar disorders such as apathy, depression, and hypersomnia. All of these phenomena are characterized by decreased motor activity, lassitude, impaired social functioning, and negative impact on stroke outcome [33].

Apathy is a common poststroke phenomenon, which is characterized by decreased motivation, limited goal-directed behavior, including its emotional component, and limited goal-directed cognitive activity. Prevalence of poststroke apathy is over 50% [34]. Apathy after stroke is associated with older age, damage to the frontal-subcortical region of the brain, and decreased cognitive function. Studies of poststroke apathy and asthenia showed that these two phenomena are not related to each other [35, 36].

Asthenia can be seen in patients with depression. However, depression is more complex phenomenon than asthenia; clinical presentation of depression includes 3 components: emotional disturbances (dysthymia, anhedonia, feeling of hopelessness), negative cognitions (self-blame and self-effacement ideas) and behavioral disorders (decreased appetite, slowness, asthenia) [37]. E. Douven et al. showed that these two phenomena are interconnected both in the acute and recovery period of stroke. However, several studies demonstrated fundamental differences between the two phenomena. In particular, only half of patients with PSA have symptoms of depression, and antidepressants (e.g. fluoxetine) can reduce the severity of depression but not asthenia; moreover, some antidepressants such as tricyclics can exacerbate asthenia [36].

Hypersomnia (daytime sleepiness) can be similar to asthenia but represents an increased likelihood of falling asleep in certain situations. Unlike hypersomnia, PSA does not improve after sleep. However, it is of note that both phenomena are associated, to one degree or another, with poststroke sleep disorders [7].

Besides pathological fatigue, some authors distinguish pathological fatigablility. The latter is a responce to increased exertion when performing certain actions due to a neurological deficit. For example, one patient with dysphasia and another patient with leg paresis would feel very tired after a normal conversation or walking, respectively. However, pathological fatigability usually is seen in combination with pathological fatigue, which is observed regardless of the exertion. Therefore, classifying pathological fatigability as a separate phenomenon is doubtful, and it is usually considered only as one of the mechanisms underlying poststroke asthenic syndrome [38].

Diagnosis of PSA usually does not require any additional investigation methods; however, if patients experience concominant symptoms (e.g. edema, bradycardia, pale skin, brittle nails, etc.) or an unusual course of asthenia, when it worsens over time, a medical condition (e.g. anemia, hypothyroidism, chronic inflammatory disease, diabetes, sleep apnea, etc.) can be suspected [7]. In such cases, patients should be screened for these conditions.

Treatment

There is an unmet medical need for patients with PSA [39]. Potentially effective therapies for PSA include psychostimulants. In particular, the randomized controlled trial (RCT) MIDAS demonstrated the efficacy of modafinil 200 mg/day [40]. However, in another RCT modafinil did not have any significant effect on MFI-20 score but improved overall score of the FSS scale and vitality subscore of the SF-36 scale. An analysis conducted in Australia showed economic benefits of modafinil for patients with PSA of working age [41]. Few open studies conducted by Russian authors demonstrated the effect of medications such as sulbutiamine, phenylpiracetam, and idebenone in the treatment of PSA [7, 39].

Literature data reported a positive effect of vitamin D supplementation in poststroke patients with asthenia and vitamin D deficiency [42]. Studies of Chinese authors showed positive effects of therapies popular in the Oriental medicine such as herbal remedies with *Astragalus membranaceus* and electroacupuncture [39].

Transcranial direct current stimulation is a non-invasive neuromodulation method based on treatment of the cerebral cortex by weak electric field. A RCT conducted by X.L. Dong et al. showed that a 4-week course of transcranial direct current stimulation significantly improved PSA vs. placebo. However, there were no inter-group differences at Month 8 [43].

Non-medication interventions for PSA also include psychoeducation, cognitive behavioral therapy, multicomponent programs, mindfulness-based stress reduction therapies [44], and complex rehabilitation [45]. A systematic review conducted by D. Tai et al. showed that exercise training reduced PSA [30]. According to the COGART RCT, the highest efficacy was demonstrated by a combination of cognitive behavioral therapy with graded physical exercise [46].

C.H. Teng et al. conducted a systematic review of patients' strategies for adaptation to PSA [47]. An important role in adaptation to PSA is played by family members, employers, and colleagues; however, the authors could not find out how close ones can contribute to this process. In the opinion of stroke survivors, PSA should be addressed by training them and their close ones on key approaches to its management.

The adaptation process includes adaptation to asthenia itself, daily activities, and the patient's role in the society with the account of the limitations associated with the stroke. In poststroke patients, asthenia has a negative impact on all areas of activities such as physical, cognitive, mental, and social functions. Therefore, a multidisciplinary team, in collaboration with the patient and their caregivers, should develop a comprehensive strategy to better adapt the patient to PSA.

Impact on stroke survivors' life

PSA has a negative impact on various aspects of stroke survivors' life and impairs their recovery from poststroke neurological deficit [48-51]. In particular, PSA in the acute period of the first stroke is a predictor of low activity of daily living at discharge [51] and 1.5 years post-stroke [50], regardless of the presence of depression. Based on the data available, the authors concluded that treatment of PSA can be considered as an option to increase the effectiveness of rehabilitation measures; however, clinical studies are needed to confirm this assumption.

PSA reduces the patient's quality of life [52, 53], instrumental activities of daily living [54], increases the risk of suicidal behavior [55], and reduces the likelihood of returning to work after stroke even in patients without significant neurological deficit [56].

Conclusion

Up to half stroke survivors have asthenic disorder. The mechanisms underlying PSA are being investigated; they are likely to be related to brain connectome damage, as well as neuroinflammatory and neuroendocrine mechanisms. To diagnose PSA, the healthcare provider should ask the patient about their symptoms such as lack of energy, lassitude, and fatigue that do not decrease after rest or sleep; differential diagnosis of PSA should include depression, apathy, and daytime sleepiness. Factors predisposing patients to PSA include female gender, older age, anxiety and depressive disorders, severe neurological deficit, sleep disorders, diabetes, etc. The most effective treatment options for patients with PSA include cognitive behavioral therapy, graded physical activity, and, in more severe cases, psychostimulants.

Further studies are needed to clarify the mechanisms underlying PSA and, based on their results, treatment options with high efficacy should be developed for patients with PSA. When planning rehabilitation in stroke survivors, it is necessary to consider the high risk of developing PSA in this population.

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