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Stress, Asthenia, and Cognitive Disorders

E. E. Vasenina, O. A. Gankina, and O. S. Levin

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Asthenia is a clinical syndrome that can be manifest in almost all somatic, infectious, and neurological diseases. Initially a protective mechanism indicating depletion of energy resources, asthenia can become a pathological and extremely disabling condition, and can even progress to an independent immune-mediated disease – chronic fatigue syndrome. Asthenia is often combined with affective and cognitive disorders, producing diagnostic difficulties. The article addresses the complex interweaving of asthenia, chronic fatigue syndrome, and cognitive and affective disorders.

Keywords: asthenia, chronic fatigue syndrome, cognitive impairment, affective disorders, treatment.

Asthenia and Chronic Fatigue Syndrome. The term *asthenia* (from the Greek *a = deprivation*, *without*, and *esthenos = cheerfulness*, *strength*) literally means *impotence*, *lack of vigor*. The clinical manifestations of asthenia are feelings of fatigue, malaise, muscle weakness, and loss of energy, usually for no apparent reason. Despite some subjectivity of the main complaints of patients with asthenia and the frequent absence of any pathological substrate for this condition, the extents of limitations and perceived disability among patients with asthenia syndrome are extremely high. Thus, about 30% of outpatient visits involve patients with main complaints of fatigue and/or exercise intolerance. This is not surprising, as the fatigue felt by a person can cause sharp mood drops, reduce social life to the level of complete isolation, and restrict work capacity and the ability to perform daily activities; these, naturally enough, are extremely significant factors that determine the quality of life and the risk of disability. Even in cases with a severe course and severe clinical signs, the disease remains undiagnosed in 20% of patients due to the nonspecific nature of complaints, while the frequent combination of asthenia with depression and other affective disorders leads to patient's conditions being regarded as functional and emotional disorders [1].

Weakness and fatigue can also occur in healthy people, but their presence is usually proportional to the intensity and duration of loading. In asthenia, there is a mismatch between the feeling of fatigue and the intensity of effort expended, i.e., a pathological fatigue threshold is formed such that minimal physical or mental stress can cause the patient to feel marked exhaustion and become unable to continue activity to the previous level (the phenomenon of intolerance to habitual actions). Triggers can be simple tasks like climbing stairs or crossing a room. Asthenia syndrome developed evolutionarily as a type of protective mechanism, signaling depletion of energy resources and the need for this to be corrected. It is therefore a characteristic feature of asthenic syndrome that it disappears after rest, as soon as the energy deficit which operated as the initiating element in pathological fatigue is compensated [2]. Asthenia has a variety of causes, including stress, various infectious diseases, acute and chronic somatic and neurological pathologies – i.e., anything whose occurrence increases the "expenditure" of energy or requires significant energy outlay for recovery will be accompanied by the development of this state.

Asthenia can be primary (for example, idiopathic or occurring on the background of a stressful situation) or secondary, when it develops on the background of an existing pathology (autoimmune, cardiovascular, neurodegenerative, or other diseases), which explains its high prevalence among both inpatients and outpatients.

A time criterion discriminates physiological (protective) weakness and exhaustion, which are elements of the recovery process after stress or illness, from pathological asthenia, which has transitioned from a recovery-promot-

Russian Medical Academy of Continuous Professional Education, Russian Ministry of Health, Moscow, Russia;
e-mail: neurolev@mail.ru.

ing mechanism to an independent disabling condition – asthenia can be diagnosed if complaints of fatigue persist for more than a month. This period either indicates inadequacy of compensatory mechanisms, which may require additional correction, or may indicate that the pathological process has acquired a chronic nature as a natural consequence of its progression. If complaints of unexplained fatigue persist for more than six months, the patient can be taken as having developed chronic asthenia, which is then more correctly called chronic fatigue syndrome (CFS) or myalgic encephalomyelitis.

It is fundamentally important to distinguish between asthenia and CFS, because CFS is not a clinical syndrome but an independent nosological pathology mediated by a persistent dysfunction of immune-mediated mechanisms [3]. Unfortunately, despite the extreme urgency of the problem of chronic fatigue, which has become of particular importance due to the ongoing COVID-19 pandemic, there are difficulties in diagnosing this condition in real clinical practice. This is due to the fact that the existing criteria for CFS are extremely insensitive, because of the non-specific nature of complaints. In addition, methods for detecting objective laboratory or instrumented biomarkers have not been developed, which leads to the risks of both overdiagnosis and low detection of patients with CFS. For a long time, the most common criteria for diagnosing this condition were the US Centers for Disease Control and Prevention (CDC) 1994 criteria. A diagnosis of CFS could be made if the patient had chronic fatigue, increasing over six months and leading to a decrease in working capacity by more than 50% of the baseline level. In addition to these obligatory criteria, the diagnostic criteria required the presence of at least four of a set of nine signs or symptoms: muscle pain, joint pain, unexplained fever, swollen lymph nodes, headaches, cognitive disorders, affective disorders, sleep disturbance, and physical fatigue.

Since 2015, following the publication of the report of the expert group of the National Medical Academy, which officially recognized CFS as an independent disease, updated criteria for diagnosing this condition have been introduced into clinical practice. These proposed recommendations require three obligatory symptoms for the diagnosis of CFS: a significant decrease in or impairment of the ability to participate at premorbid activity levels, post-exercise malaise, and unrefreshing sleep. These three key manifestations must be combined with one of two proposed additional criteria – cognitive impairment or orthostatic hypotension (OHT) [4]. It should be noted that the revision of the diagnostic criteria unfortunately not only did not improve the quality of diagnosis, but, on the contrary, led to an increase in the number of cases of both false positive and false negative diagnoses of CFS. This is largely due to exclusion of "inflammatory" signs confirming the pathogenetic nature of CFS, which were more clearly defined in the CDC criteria. The symptoms proposed for diagnosis on the 2015 criteria do not distinguish between CFS and asthenia within the framework of primary affective disorders, because of their low sensitivity and specificity. Furthermore, a large number of reports have appeared describing atypical variants of the course of CFS, when the clinical picture is either dominated by non-standard manifestations or there is an incomplete range of the symptoms required for making a diagnosis. Thus, despite the fact that chronic fatigue is an obligatory and integral criterion for establishing the diagnosis, modern epidemiological studies confirm the classical variant of the course of illness, with all symptoms, in only 0.2–0.7% of patients. Patients with a confirmed diagnosis of CFS may display dominance of dysthymia or functional somatic disorders, while in some cases the disease may manifest predominantly as anxiety symptoms with movement avoidance behavior, which is extremely difficult to distinguish from the signs of primary astasobasophobia. The individual clinical phenotypes of CFS can apparently be explained by the different structures involved in the pathological process, as well as by the characteristics of disease progression, though currently there is neither a clear classification nor a developed structure for diagnosing individual forms [5].

The Complex Interweaving of Asthenia, Chronic Fatigue Syndrome, and Affective Disorders. As noted above, asthenia and CFS may be primary (idiopathic) or may be associated with various somatic or neurological pathologies, i.e., develop secondarily on the background of an underlying disease. However, even when the underlying cause cannot be identified and chronic fatigue and pathological fatigue appear to be developing in isolation, there are generally psychoemotional stress and overstrain factors, which most often act as the starting point for the development of clinical symptoms.

The relationship between stress, asthenia, and the subsequent development of CFS has several explanations. First, stress and the stress response are extremely energy-intensive. Activation of the sympathetic-adrenal system should, in evolutionary terms, provide the body with the opportunity to mount the fastest possible physical reaction in response to threatening and dangerous situations – this is perceived as a stress factor, i.e., the "fight or flight" principle. This is ensured by activity in limbic system (telencephalon) structures, i.e., the amygdala, which, having perceived a threatening stimulus, launches all other processes by activating the autonomic centers and the sympathetic nervous system. Despite the fact that these reflex physical responses to stress are suppressed by neocortical activity in modern humans and most negative emotional reactions are not accompanied by immediate physical stress responses, the processes providing "fight or flight" ability (increases in blood pressure, blood flow to muscles, breathing, insulin release, etc.) are still activated. Initiation of catabolic processes as part of the stress response inevitably requires replenishment of energy resources and activation of anabolic reactions, which explains the link between stress and asthenic syndrome. This in turn provides an explanation for the frequent

comorbidity of affective disorders with the phenomena of asthenia – in both cases, stress acts as a key initiating factor. There are different possible variants: chronic fatigue may be part of the clinical manifestations in patients with primary affective disorders, or, conversely, affective symptoms may be among the manifestations of CFS and severe asthenia.

The comorbidity of these two pathological conditions is confirmed by studies of the risk of developing asthenia in pilots depending on the distance of flights. Thus, 76.5% of short-haul pilots, who have higher frequencies of take-offs and landings, and, thus, larger numbers of presumptive stress factors, experienced phenomena of extremely pronounced exhaustion, and this was significantly greater than the number of complaints of chronic fatigue among long-haul pilots, where the level of emotional loading was objectively lower. In addition, the incidence of clinically significant anxiety in short-haul pilots was higher, which confirms the close relationship between asthenic and affective symptoms [6].

Due to the fact that the commonality of mechanisms determines the frequent combination of CFS, depression, and anxiety, it is often difficult to identify the primary pathological process. Decreased performance, tiring, and fatigue are among the symptoms pointing to depression, while disturbances in emotional responses, decreased mood, and lack of motivation are part of the structure of CFS and asthenic disorders. These two pathological conditions (major depressive disorder (MDD) and CFS), having a similarity of primary initiating pathological processes, appear then to "diverge" depending on which CNS structures are dominant in mounting responses to metabolic and inflammatory changes. This also determines the dominant defect and the individual features of clinical symptoms.

Functional MRI studies have made it possible to show that there is a decrease in global cortical blood flow in the frontal, temporal, parietal and occipital lobes in CFS, deteriorating further on the background of maximum physical exercise. This appears to be due to impairment of the activity of the ascending reticular formation, which regulates the level of wakefulness and is required for initiation of any active processes in the CNS; this may be the cause of exhaustion and aggravation of weakness in patients with CFS occurring on additional loading. This is confirmed by the brainstem hypoperfusion demonstrated by single-photon emission computed tomography, which correlates with the severity of the manifestations of pathological fatigue and the characteristics of the clinical symptomatology. Bottom-up influences regulate the level of attention, which in turn mediates activation of cortical zones. Disruption of the brainstem can also explain the imbalance of the sympathetic and parasympathetic divisions of the autonomic nervous system, which leads to the development of orthostatic hypotension (OHT), which is an impairment of the adaptation of the cardiovascular system when changing body position and moving to the vertical, and this may be an additional factor in exercise intolerance.

Along with depletion of cerebral blood flow in patients with CFS, changes are observed indicating increased lactate levels and reduced glucose metabolism, apparently associated with inflammatory activation of microglia and impairment to their trophic functions. Functional neuroimaging data indicate that patients with MDD have changes to the functioning of the same areas of the cortex as in CFS, with the exception of the frontal lobe: its dorsolateral regions are predominantly affected in CFS, while the orbitomedial zone of the prefrontal cortex, which is traditionally associated with the regulation of behavior, is affected in MDD. However, the isolated involvement of the cortex and the absence of a significant decrease in blood flow in the brainstem in patients with depression suggest that hypoactivity of the cortical regions in this case is primary and is associated with a decrease in the activity of the gray matter itself and not with impairment at the level of the regulation of nonspecific bottom-up influences.

Thus, despite the similarity of the clinical manifestations, the pathological processes in CFS and MDD differ both in mechanism and in terms of the structures involved, so thorough clinical assessment with mandatory identification of the primary pathological condition is required. When pathological fatigue is combined with disorders of the emotional domain, it is important to identify what appeared first, what was added during the course of the disease, and what determines the maximum degree of restrictions – this approach allows more differentiated selection of therapy and individualization of approaches to the management and rehabilitation of such patients [7].

It should be noted that there is another extremely significant factor that explains the association of CFS with depression – this is inflammation and changes in immune-mediated responses. The stress factor plays an equally important role here too. The paraventricular nucleus of the hypothalamus (PVN), being the key stress center of the brain, receives and processes information and responds to a wide range of physiological reactions, controlling the neuroendocrine and autonomic components of the response. Activation of the sympathoadrenal axis triggers the release of proinflammatory cytokines, as immune mechanisms are modeled by the activity of the sympathetic nervous system, which is part of the body's overall response to threat (readiness for damage). Persistent inflammatory responses with constant production of cytokines and chemokines can switch the hypothalamic PVN into a persistent dysfunctional mode, which can subsequently lead to dysregulation of the immune response, with permanent activation. Thus, patients with CFS show pathological expression of tumor necrosis factor-alpha, transforming growth factor-beta, and interleukins (IL)-2 and -4, which are important proinflammatory cytokines [8].

Another cause of immune imbalance is impairment of anti-inflammatory processes: in health, the second vector of the body's stress response suppresses the triggered proin-

flammatory activity, i.e., the hypothalamic-pituitary axis is activated, with release of cortisol. Glucocorticosteroids (GCS) initiate anabolic processes aimed at restoring energy expenditure and also suppress the activity of the induced immune response by releasing anti-inflammatory cytokines, which act as classical immunosuppressants. Asthenic and affective disorders are closely associated with reduced cortisol levels, which apparently determine the low activity of anti-inflammatory cytokines and, as a result, persistent immune activation. A number of studies have shown that patients with CFS have not only low corticosteroid release, but also an altered response to corticosteroid stimulation. This suggested that the long-term inflammation and activation of immune-mediated mechanisms in patients alters receptor sensitivity, forming resistance. Thus, a permanent inflammatory process is formed as a result of impairment to the immune activation suppression system. Changes in the sensitivity of GCS receptors are believed to be a key pathogenetic link in the transition of asthenic syndrome to CFS, a separate nosological form of an immune-mediated disease. The chronic inflammatory process not only increases the risk of pathological fatigue and depression, but also has a significant association with the severity of the clinical symptoms, which has been confirmed by a large number of studies [6, 8].

Another link between affective disorders and chronic fatigue is microglia. In vivo studies have shown that activation of glial cells by immune complexes leads to the appearance of clinical signs of depression in animals. A close association between the manifestations of fatigue and signs of inflammatory activation of microglia has been confirmed. The most vulnerable zones are areas of the hypothalamus and the closely related limbic system, as confirmed in 2014 by studies using positron emission tomography and MRI. Thus, the inflammatory activity of microglia was noted predominantly in the cingulate gyrus, hippocampus, amygdala, and thalamus. The involvement of the limbic system in this process is an additional factor in the formation of both affective and cognitive disorders. Moreover, some inflammatory cytokines, with direct neurotoxic effects, may contribute to disrupting the functions of the main clusters of neurons (the nuclei of neurotransmitter systems) by increasing oxidative stress and metabolic abnormalities, causing significant neurotransmitter derangements, which also creates conditions for the formation of neuropsychiatric symptoms [8, 9].

The association of chronic fatigue and pathological fatigue with various past bacterial and viral infections is explained by their inflammatory nature [10]. Thus, outbreaks of a disease resembling CFS after nosocomial and epidemic infections have been seen throughout the 20th century. Although there were then no specific criteria for asthenia, the symptoms described in the literature – fatigue, lethargy, malaise, sleep disturbance, and decreased concentration, often aggravated by exercise or stress – are very similar to the condition now regarded as CFS [11, 12]. The development of asthenia or CFS in the post-infectious period is most commonly a complication of infectious mononucleosis, caused by Epstein–Barr virus, though similar symptoms are also recorded after other viral infections, as well as mycoplasma pneumonia, giardiasis, and even after some subtypes of infection caused by fungi of the genus *Candida*. Significant increases in the numbers of cases of post-infectious asthenia and CFS occur during epidemics. Thus, after the 1918 flu pandemic, 40% of those who recovered from the disease had fatigue, lethargy, and impaired concentration, with increases in severity after physical exertion. Similarly, in 2009, increases in the incidences of CFS and asthenia were found in Norway after the H1N1 influenza pandemic. Apart from the association with previous influenza, CFS was associated with outbreaks of coronavirus infection in 2002 and 2012 [8, 13, 14].

Along with fatigue following influenza and coronavirus epidemics, many patients experienced mental and neurocognitive impairments. Thus, the Spanish flu epidemic in 1918 was followed by a 7.2-fold increase in the number of primary hospitalizations for mental disorders, this lasting several years, in patients with acute respiratory distress syndrome on the background of H1N1 influenza; high levels of anxiety and depression a year after infection amounted to 50% and 28% respectively. Patients with a history of SARS or MERS had high prevalences of depression (14.9%) and anxiety (14.8%), compared with rates in the general population (about 7%) [15].

COVID-19 is undoubtedly a trigger for the development of fatigue. One study showed that 17.5% of patients had CFS after coronavirus infections. Various asthenic manifestations are noted in almost 100% of cases. There have been significant increases in the prevalences of anxiety and depression in parallel with this. Despite the fact that the negative dynamics of affective disorders can be explained in part by the actual conditions in which the pandemic occurred – social isolation, the general tension of the situation – the close relationship with asthenia and inflammation may also be an important trigger factor that has to be taken into account [16].

The Complex Interweaving of Asthenia and Cognitive Disorders. Cognitive impairment is an important clinical manifestation of CFS and is among the diagnostic criteria. The 2015 diagnostic criteria include cognitive disorders in the framework of CFS as impaired thinking, along with difficulties in synthesizing and processing information, which can be characterized as a classical dysregulatory deficit [17, 18]. In addition, there are deficits of attention and working memory and a general slowness of neuropsychological processes (neurodynamic disorders). One feature of cognitive disorders in CFS is their significant variability and dependence on loading, tension, effort, and even body position, which is apparently associated with OHT and impaired cerebral perfusion on transfer to the vertical position. It should be noted that cognitive dysfunction very

often comes to the fore among patients' complaints as, in conditions of studying and performing intellectual activity, it is precisely the limitation to adequate cognitive functioning that can determine the greatest level of disability in patients [19].

Affective disorders constitute an additional factor in the development of cognitive symptoms and the association with CFS. In stress situations and anxiety, cognitive processes switch to the exclusive perception of threatening stimuli, which makes it difficult to acquire any neutral and positive information. This is achieved by shifting activity between the hippocampus and the amygdala, which is regulated through GCS receptors. Inflammation and stress lead to functional shutdown of the hippocampus, thereby disrupting memory processes [20].

As with affective disorders, it can be difficult in clinical practice to distinguish between primary cognitive impairment and the symptoms that may develop when a patient has CFS. Patients with moderate cognitive impairment may complain of exhaustion, difficulty concentrating, and slowness and fatigue when performing mental work, which is associated with a significant increase in the cost of mental activity in a progressive and increasing deficit. Therefore, it is also very important here to seek the cause without forgetting the need to assess cognitive status in patients with complaints of chronic fatigue or the need to identify pathological fatigue in patients with cognitive symptoms, especially if they are young people [21]. The relationship between asthenia and cognitive disorders should also be noted because of the increased risk of delayed neurodegenerative changes, which are significantly more common in patients with CFS [8], though this is relevant for older people.

Recent research in psychoneuroimmunology has shown that neuroimmune dysregulation has profound effects on neuron function and viability. At the molecular and cellular levels, these processes lead to changes in the functioning of peripheral and cerebral immune cells, with increases in the quantities of proinflammatory mediators. Neuroinflammation generally fades over time with the restoration of homeostasis; however, persistent dysregulation is associated with chronic neuroinflammatory processes and underlies a number of neurological diseases [22, 23]. Neuroinflammation is an important link in the development of the neurodegenerative process, as illustrated by the examples of Alzheimer's, Parkinson's, and Huntington's diseases and multiple sclerosis. In this situation, CFS may be an intermediate stage of a chronic neuroinflammatory disease that occurs in the absence of CNS pathology, though it may increase the risk of developing neurodegenerative pathology in the future [24, 25].

The risk of developing neurodegeneration in CFS is also associated with the fact that the genesis of CFS is a dysfunction of the glymphatic system, which impairs the elimination of toxins from the CNS, which in the long term can lead to the accumulation of pathological protein molecules and CNS metabolic products in the intercellular and cellular space and subsequent neuron death [26, 27]. Practical studies of this hypothesis led to some patients with CFS undergoing experimental lumboperitoneal shunting to improve sanitation of the cerebrospinal fluid and facilitate the work of the glymphatic system, but because of the invasiveness of the procedure and the lack of convincing data on its effectiveness, these studies are currently more of theoretical interest than practical [28]. Cerebral hypoperfusion probably also plays a role in the development of delayed neurodegeneration in patients with CFS, which is particularly critical for elderly patients because of the high risk of already-present functional neurological failure [29, 30]. The tendency to accumulate trace elements, namely iron, is also often found in neurodegenerative diseases. Results from a number of studies have indicated that the ratio of parameters of MRI T1 weighted/T2 weighted image parameters (T1w/T2w) can reveal a significant increase in the content of myelin and/or iron in patients with CFS in the subcortical gray matter, brainstem,and white matter projection tracts involved in sensorimotor communication, in the sensorimotor gyri of the white matter, and the subcortical structures of gray matter associated with motor control, as compared with a control group. The highest T1w/T2w ratios were recorded in the globus pallidus, which has a high iron content [31].

In addition to the direct connection between CFS and neurodegeneration, some of the complaints presented by patients may initially mimic CFS and hide the onset of neurodegenerative pathology [32]. It is therefore particularly important for elderly patients with cognitive and affective disorders which can develop both as part of and independently from CFS to undergo neuropsychological testing and detailed neurological examination to ensure prompt diagnosis of the possible onset of neurodegenerative disease [33].

Therapy for Asthenia/Chronic Fatigue Syndrome. There are as yet no standard treatments for CFS. Commonly used treatments include immune-boosting drugs, lifestyle modification, cognitive behavioral therapy, local physical therapy, and graduated exercise therapy. The main goals of treatment are to relieve the symptoms of CFS, improve psychological well-being, and restore social behavioral functions [34, 35]. Taking account of the fact that the activity of the ascending reticular formation is disturbed in CFS, provoking decreases in the activity of cholinergic structures, in particular the nucleus of Meynert, compensation for acetylcholine deficiency seems to be a very important direction in the treatment of CFS [36]. It is, after all, cholinergic deficit that mediates the attention deficit and neurodynamic cognitive disorders most typical of patients with CFS. Thus, studies reported in 2018 showed that treatment with choline esterase inhibitors not only leads to improvements in cognitive performance, but also contributes to significant reductions in the manifestations of cognitive exhaustion, one of the key symptoms of chronic fatigue, as compared with placebo [37]. The study was conducted on patients with

Alzheimer's disease; it goes without saying that basic anti-dementia therapy cannot be advised for patients without dementia, even despite such encouraging results.

There are other ways to correct cholinergic imbalance, in particular the use of choline donators. Choline alfoscerate, an acetylcholine precursor, compensates for choline deficiency and acts as a cholinomimetic. In addition, choline alfoscerate metabolism forms glycerophosphate, which is then transformed to phosphatidylcholine, an important structural component of cell membranes. Thus, use of choline alfoscerate in clinical practice produces symptomatic effects and improves cognitive processes by correcting the deficit of cholinergic influences on the one hand, and, on the other, has a neuroprotective effect due to stabilization of cell membranes and reductions in the risk of secondary neurodegenerative changes in patients with CFS. The efficacy of choline therapy with alfoscerate has been confirmed by results from placebo-controlled trials, which have demonstrated significant improvements in assessments on neuropsychological scales, including for those neurodynamic parameters reflecting severe asthenic manifestations and chronic fatigue [38]. Choline therapy with alfoscerate also offers hope for improvement in mood disorders, another common comorbid condition in patients with CFS. Thus, in comparison with placebo, patients receiving active therapy showed decreases in the severity of depression and improvements in emotional responses [38].

The choline alfoscerate formulation Cereton has an extensive evidence base, and its efficacy has been demonstrated in correcting cognitive and affective disorders [39, 40]. In addition, studies using genetic testing and biomarker determination have shown it to have neuroprotective potential [39], such that Cereton can be confidently recommend for the complex therapy of patients with CFS.

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