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Experimental Medicine

Electromyographic Indicators of Sarcopenia in Elderly Men with Subclinical Cognitive Dysfunction

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Sarcopenia is caused by loss of skeletal muscle mass and decreased function. This is due to a decrease in the number of muscle motor units and an increase in the size of the remaining motor units, which is due to the function of reinnervation of the denervated fibers assigned to them. There is no evidence to support the extent of motor unit remodeling in individuals with sarcopenia. The aim of the study was to compare parameters and numbers of motor units in young (n=20), older non-sarcopenic (n=15) and sarcopenic men (n=30). The study was carried out using a Keypoint electromyograph from Metronik. Both needle and surface electrodes were used. The number of motor units was reduced in all groups of older people compared to young people ($p < 0.001$), and their duration was increased in men without sarcopenia. The results suggest that sarcopenia is preceded by motor unit remodeling. The reinnervation process increases motor unit parameters in older adults with nonsarcopenic muscles, which does not occur in older adults with sarcopenia. Based on all of the above, we can conclude that the absence of increased motor unit parameters distinguishes sarcopenic muscles from non-sarcopenic muscles. Our data can be used for early diagnosis and treatment of subclinical cognitive dysfunction. *© 2024 Bull. Georg. Natl. Acad. Sci.*

dementia, sarcopenia, ENG

Dementia is a cognitive dysfunction that significantly alters person's daily activities, usually involving problems with memory, thinking, and behavior. We should especially emphasize emotional problems and decreased motivation. Dementia has a significant impact on the individual, the caregiver, and their social relationships. This, in turn, is a global burden, the overcoming of which is important not only for the patient's family, but also for the entire country.

The International Classification of Diseases classifies dementia as a neurocognitive disorder, which has many forms and subclasses. Among the various forms of dementia, the most common is Alzheimer's disease, or a neurodegenerative disease [1].

Dementia can be associated with Parkinson's disease, vascular diseases, HIV infection, prion diseases with Lewy bodies. It can also be manifested by tauopathy and synucleinopathies [1,2].

The greatest risk factor for developing dementia is old age, although it is not considered a normal part of aging. Many people over the age of 90 have no signs of dementia.

Currently, dementia is the 7th leading cause of death. Every year, 10 million new cases of the disease are reported worldwide, one every 3 seconds [2].

Dementia is characterized by a clear motor dysfunction that significantly reduces the quality of life, although it is under-estimated and depends on the subjective evaluation of symptoms. Motor symptoms are not part of the neurocognitive domain but precede cognitive decline in Alzheimer's patients. Today, there is no doubt that dementia includes not only cognitive but also motor components. Adequate attention is not paid to the motor symptoms of Alzheimer's disease, which in turn greatly affects the quality of life [1,2]. Objective screening methods remain subject to criticism and are also difficult to access.

Motor impairments in dementia are both central (frontal lobe disinhibition) and peripheral (resulting from skeletal muscle dysfunction), resulting from collagen binding and intramuscular inflammation. All this makes possible the objective and quantitative assessment of motor disorders during dementia, using electrophysiological methods (EMG), which will allow us to develop other instrumental screening methods to assess the presence and severity of dementia, in addition to the reduction of cognitive symptoms. In particular, the development of an EMG-based method for the objective determination of motor disorders in patients with dementia, which will be the basis for determining the role of neuromuscular system dysfunction in the pathogenesis of dementia.

Sarcopenia, a common phenotype of aging, is defined as a progressive and generalized disease of skeletal muscle accompanied by accelerated loss of muscle mass and function. Sarcopenia is associated with increased adverse outcomes, including falls, functional decline, frailty, and mortality. Several cross-sectional studies have shown that sarcopenia may be a good indicator of poor cognitive function and dementia. However, the association of sarcopenia with cognitive function and risk of dementia has not been convincing in longitudinal studies [3,4]. A study among Japanese community-dwelling older adults found that sarcopenia was an independent risk factor for cognitive decline over the 1-year study period. On the other hand, two cohort studies involving French women and older Korean men did not find a significant association between sarcopenia and mild cognitive impairment (MCI). More research is urgently needed, especially in developing countries where the burden of cognitive impairment is rising sharply [4].

The pathogenesis of sarcopenia is still unclear and is associated with immobility, obesity, and oxidative stress affecting muscle mass and function.

There is evidence in the medical literature that separates cognitive and motor impairments in dementia. Since about 2021, specialist literature has emerged showing that sarcopenia is associated with cognitive dysfunction. Although the exact mechanism associated with sarcopenia and cognitive dysfunction has not yet been determined [4-6]. Several studies have shown that skeletal muscle produces and releases molecules called myokines, which regulate brain functions including mood, learning, motor activity and protect neurons. Studies have shown that the “talk” or myocerebral junction connection, as well as studies conducted on physical education, have confirmed the existence of the said connection, in particular, physical activity changes the level of circulating myokines, and the latter has a positive effect on brain function [5, 7,8].

Aging alters skeletal muscle homeostasis, disrupting the balance between cell regeneration and differentiation, as well as the rate of protein synthesis and regeneration. The number of stem cells in the second muscle fibers decreases. This is due to the proliferation and differentiation of second muscle cells. The hypothesis that decreased satellite cell activity causes sarcopenia is unclear.

With age, the rate of protein synthesis and the ability of the proteolysis system decrease, leading to decreased skeletal muscle function. In sarcopenia, an important role is also played by changing the pathogenic relationship between adipose tissue and muscle. In sarcopenic muscles, the oxidative capacity of mitochondria is reduced [7,8].

Sarcopenia is considered a risk factor for cognitive decline. It is well established in the literature that sarcopenia increases the risk of cognitive decline. Decreased muscle mass is considered a predictor of cognitive dysfunction. Exercise has also been shown to improve brain function by increasing the volume and improving the function of the prefrontal cortex, the hippocampus, which is an area of neurons associated with memory and cognition [7,9]. Some authors indicate that the risk of developing dementia in people involved in physical activity is 30-40% lower than in sedentary people. Exercise regulates the expression of myokines and helps regulate muscle metabolism [9].

Myokines have created a new paradigm and conceptual framework for understanding the cross-talk between muscles and other organs and tissues. Skeletal muscle has been identified as an endocrine organ with a high capacity to secrete myokines.

Myokines are cytokines and other peptides produced during muscle contraction and exhibit autocrine, paracrine and endocrine effects.

Recent studies have identified over 600 myokines, however, their specific bioactivity remains undescribed and poorly understood [8,9].

Myokine is involved in muscle proliferation, regeneration and differentiation. Myokine signaling mediates the endocrine muscle-brain loop and facilitates muscle-brain communication.

Myokine FNDC5, just like irisin, the level of which increases after exercise, stimulates proliferation, differentiation of neurons, and also increases its level in the hippocampus, irisin increases brain-derived neurotrophic factor, which plays an important role in cognitive functions. The brain-derived neurotrophic factor BDNF increases in response to exercise, and its levels also increase in skeletal muscle. BDNF affects the activation of cognitive functions, increases the number of cells in the dentate gyrus of the hippocampus, and is involved in neuronal differentiation and plasticity, which

Table. Mechanisms of action and effects of myokines on the brain

Myokine	Effects on the brain	Mechanisms of action
FNDC5/Irisin	Neuronal proliferation and differentiation, synaptic function, memory	PKB and ERK1/2 signaling pathway
Cathepsin B	Neurogenesis, memory, Learning	BDNF synthesis
BDNF	Synaptic plasticity, neuronal differentiation, cell survival, hippocampal function	PI3K and ERK signaling pathway
IGF1	Neurogenesis and neuron survival, neurotrophic, angiogenic, and metabolic proprieties survival and differentiation	BDNF synthesis
IL-6	Further investigation are needed	To be investigated
LIF	Astrocyte's development, oligodendrocytes survival amyloid β-induced neurotoxicity	AKT/extracellular signal-regulated-mediated c-fos induction
L- Lactate	Memory, learning, neuroprotection, neuronal plasticity, neuronal metabolism, LTP maintenance, angiogenesis	BDNF synthesis; Hydroxycarboxylic acid receptor 1 (HCAR1); VEGF synthesis; NMDA glutamate receptor-mediated signaling; Arc, c-Fos, and Zif268 synthesis

FNDC5 – Fibronectin type III domains containing protein 5; BDNF – Brain-derived neurotrophic factor; IGF1 – Insulin-like growth factor1; IL6- Interleukin 6; LIF – Leukemia inhibitory factor; PKB – protein kinase B; ERK1/2 – extracellular signal-regulated kinases ½; PI3K – Phosphoinositide 3-kinase.

clearly improves cognitive functions. BDNF also reduces the production of toxic beta-amyloid peptides, which play an important role in the pathogenesis of Alzheimer's disease. Patients with Alzheimer's disease have low levels of BDNF [7-9].

Epidemic evidence suggests that sarcopenia is associated with accelerated cognitive changes and leads to cognitive decline [6]. The exact mechanism between sarcopenia and cognitive impairment is not well understood, but it has been shown that there is a myokine-mediated endocrine loop. Myokines are factors produced by muscles that improve brain functions such as cognition, memory and motor coordination. Sarcopemia is associated with a decrease in the regenerative capacity of skeletal muscle cells and a change in the rate of regenerative reinnervation of cells. This can lead to a decrease in the secretion of mycins, which negatively affects brain function [9,10].

There are several versions for the association between sarcopenia and cognitive impairment. First, sarcopenia and cognitive impairment have similar risk factors, namely inflammation, characterized by interleukin-6 (IL-6) and tumor necrosis factor-α; oxidative stress; hormonal changes; and malnutrition. In particular, obesity in sarcopenia may affect cognitive function largely due to malnutrition. Second, skeletal muscle can produce and secrete molecules called myokines, which regulate brain functions such as learning and motor activity. Physical inactivity associated with sarcopenia also affects cognitive function by altering the levels of circulating myokines. Third, frailty allows sarcopenia to influence cognitive impairment. Frail people have deficits in executive control, particularly in the frontal cortex, which increases the likelihood of motor and executive functioning disorders [7,9,10].

Current evidence suggests that motor impairment precedes cognitive dysfunction. According to the data described above, myokine-derived compounds can be used in the treatment of neurodegenerative diseases.

Methods

Study Population: All participants were young (n=20), non-sarcopenic older (n=15) and sarcopenic (n=30) men from Georgia, aged from 18 to 40 years old and older group: 60-80 years old.

Assessment of Cognitive Function and Dementia Risk Score: We assessed cognitive functioning along four dimensions: orientation; attention and calculation; episodic memory; and visuospatial abilities. To assess the dementia risk score we used the Montreal Cognitive Assessment (MoCA) scale.

Assessment of Sarcopenia: Sarcopenia was defined as low muscle mass plus low muscle strength or low physical performance.

Measuring muscle mass: We used appendicular skeletal muscle mass (ASM) to estimate muscle mass.

$$\text{ASM} = 0.193 \times \text{body weight} + 0.107 \times \text{height} - 4.157 \times \text{gender} - 0.037 \times \text{age} - 2.631$$

Body weight, height, and age were measured in kilograms, centimeters, and years, respectively. As for gender, men were given a value of 1. Based on the ASM value, we calculated muscle mass adjusted for height.

$$\text{Height-adjusted muscle mass} = \text{ASM}/(\text{height})^2.$$

We used a dynamometer to measure muscle strength. Participants were asked to try as hard as they could to squeeze the dynamometer at a right angle for a couple of seconds and then release it, alternating the two measurements with their right and left hands. We used the mean to indicate participants' grip strength if they completed the measurement twice.

Walking speed was used to measure physical performance. To determine walking speed, participants were asked to walk 2.5 m twice at a normal pace. Participants were defined as having low physical performance when their walking speed was less than 1.0 m/s.

Covariates included demographic factors (age, gender, marital status, education, place of residence), health status, body mass index (BMI), number

of medical conditions, and lifestyle (smoking status, alcohol consumption). Education was classified as school experience or illiteracy. Place of residence was categorized as currently living in a rural area or a city/town. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to measure participants' depressive symptoms. The diseases included high blood pressure, diabetes, cancer, lung disease, heart problems, stroke, arthritis, liver disease, kidney disease, digestive disease and asthma. All covariates were reported to be associated with cognitive function or risk of dementia.

Electromyography. The study was carried out using a Keypoint electromyograph from Metronik. It was carried out using both needle and surface electrodes.

Discussion

Participants with sarcopenia were more likely to be older, live in rural areas, have less school experience, suffer from more medical conditions, and have lower BMI and CES-D scores. Participants with sarcopenia had significantly lower cognitive function.

Patients with sarcopenia had significantly lower cognitive performance. Participants with low muscle mass, low muscle strength, or low physical performance had significantly lower cognitive function. After adjusting for more covariates such as marital status, education, place of residence, CES-D, BMI, number of medical conditions, smoking, and alcohol consumption, the above associations remained.

In some studies, researchers found that participants with sarcopenia at baseline were associated with a higher risk of Alzheimer's disease (AD) and MCI [6,7,10]. One recent systematic review and meta-analysis assessed the association between sarcopenia and MCI and found a significant association between these pathologies [6,7]. However, one study of women aged 75 years and older in France did not find a significant association of sarcopenia with cognitive disfunction [6,7]. The following several factors may explain the observed differences: 1. different rates of sarcopenia and cognitive function/dementia; 2. different coverage of age groups; and 3. different follow-up periods.

In old age, sarcopenia is caused by a progressive loss of skeletal muscle mass and function. This is likely due to a significant decrease in the number of motor units innervating the muscles and an increase in the size of the remaining motor neurons, which leads to reinnervation of denervated fibers. To date, there is no convincing evidence of motor unit remodeling in individuals with sarcopenia [10]. The aim of our study was to compare the size and number of motor units in young, non-sarcopenic older and sarcopenic men. In all elderly people, compared to young people, a decrease in the number of motor units was noted. Motor unit duration was longer in non-sarcopenic men than in younger men, but this was not observed in older men with sarcopenia. The results suggest that motor unit elongation precedes muscle loss and the onset of sarcopenia. Reinnervation of denervated muscle fibers increases motor unit lifespan in non-sarcopenic adults, but not in sarcopenic adults.

Sarcopenic muscles are not characterized by an increase in the duration of motor units, which distinguishes them from non-sarcopenic muscles, which always show an increase in motor unit parameters with age [11,12].

Motor unit potential duration is markedly increased in relatively healthy older adults compared to younger adults, but motor unit potential duration is decreased in men with sarcopenia compared to healthy older adults. These data suggest that in healthy older men, muscle fiber reinnervation occurs to compensate for the reduced number of motor units, which is not observed in men with sarcopenia and leads to decreased muscle size and strength.

A decrease in the number of motor units with age has been confirmed at autopsy by counting neurons in the anterior horn of the spinal cord [12,13]. Around the same time, intravital muscle EMG techniques revealed a decrease in the number

of motor units with age. The increase in motor unit duration is due to the branching of motor neurons in denervated muscle fibers for their reinnervation. Successful reinnervation determines a decrease in the progression of muscle atrophy and sarcopenia. Little is known about the relationship between motor unit remodeling and sarcopenia. Until approximately 2015, only superficial electroneurography was used for this purpose, which did not provide information about the parameters of the remaining motor units[13,14]. Therefore, the aim of our study was to compare the size and number of motor units in young, sarcopenic, non-sarcopenic, and pre-sarcopenic older adults using needle EMG.

A decrease in the number of motor units was expected in young and healthy older men, men with sarcopenia, i.e. the loss of muscle mass would be proportional to the decrease in motor units. It was expected that the number of motor units would decrease, but their parameters would increase with age.

Conclusion

We show that motor unit losses occur relatively early in the aging process and contributes to the development of sarcopenia. Evidence suggests that expansion of surviving motor units provides a regulatory mechanism for maintaining muscle mass. It is important to note that those with sarcopenia were distinguished from men with pre-sarcopenia by their inability to increase motor unit size. Overall, our results indicate that both motor neuron loss and reinnervation of reinnervated muscle fibers from surviving motor nerve branches are critical determinants of sarcopenia progression.

ექსპერიმენტული მედიცინა

სარკოპენიის ელექტრომიოგრაფიული მაჩვენებლები სუბკლინიკური კოგნიტური დისფუნქციის მქონე ხანდაზმულ მამაკაცებში

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სარკოპენია გამოწვეულია ჩონჩხის კუნთების მასის დაკარგვით და ფუნქციის დაქვეითებით. ეს დაკავშირებულია კუნთების მოტორული ერთეულების რაოდენობის შემცირებასა და გადარჩენილი მოტორული ერთეულების ზომის ზრდასთან, რასაც განაპირობებს მათზე დაკისრებული დენერვირებული ბოჭკოების რეინერვაციის ფუნქცია. არ არსებობს მტკიცებულება რომელიც დაადასტურებს მოტორული ერთეულების რემოდელირების მასშტაბს სარკოპენიის ინდივიდებში. კვლევის მიზანი იყო მოტორული ერთეულების პარამეტრებისა და რაოდენობის შედარება ახალგაზრდა (n=20), არასარკოპენიულ ხანდაზმულებსა (n=15) და სარკოპენიული კუნთების მქონე მამაკაცებს შორის (n=30). კვლევა წარმოებდა მეტრონიკის ფირმის Keypoint ელექტრომიოგრაფით. გამოყენებული იყო როგორც ნემსისებური, ასევე ზედაპირული ელექტროდები. მოტორული ერთეულების რიცხვი შემცირებული იყო მოხუცების ყველა ჯგუფში ახალგაზრდებთან შედარებით ($p<0,001$), ხოლო მათი ხანგრძლივობა უფრო გაზრდილი იყო არასარკოპენიულ მამაკაცებში. შედეგების მიხედვით შეიძლება ვივარაუდოთ, რომ მოტორული ერთეულების რემოდელირება წინ უსწრებს სარკოპენიას. რეინერვაციული პროცესი ზრდის მოტორული ერთეულების პარამეტრებს არასარკოპენიული კუნთების მქონე ხანდაზმულებში, რაც არ ვლინდება სარკოპენიის მქონე ასაკოვნებში. ყოველივე ზემოთ აღნიშნულის მიხედვით, შეიძლება დავასკვნათ, რომ მოტორული ერთეულების გაზრდილი პარამეტრების არარსებობა განასხვავებს სარკოპენიულ კუნთებს არასარკოპენიულისაგან. ჩვენი მონაცემები შეიძლება გამოყენებულ იქნეს სუბკლინიკურად არსებული კოგნიტური დისფუნქციის ნაადრევი დიაგნოსტიკისა და მკურნალობისათვის.

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