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PHYSICAL ACTIVITY AND AMYOTROPHIC LATERAL SCLEROSIS

Osman Sinanović[1], Muhamed Lepuzanović[2] & Edin Bašagić[2]

[1]Medical Faculty, University of Tuzla, Tuzla, Bosnia and Herzegovina
[1]Sarajevo Medical School, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina
[1]International Academy of Science and Arts of Bosnia and Herzegovina
[1]Academy of Medical Sciences of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina
[2]Department of Neurology, Cantonal Hospital Bihać, Bihać, Bosnia and Herzegovina

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SUMMARY

Motor neuron diseases (MNDs) are a group of relatively rare, progressive neurodegenerative conditions (with amyotrophic lateral sclerosis/ALS being the most common) characterized by degeneration of upper and lower motor neurons leading to motor and extra motor symptoms. The etiology of MND is believed to involve complex interactions of environmental, lifestyle, and genetic factors, but so far only a few convincing risk factors have been established. Several putative risk factors associated with sporadic cases have been suggested, including repetitive blows to the head and traumatic brain injury. ALS is considered a sporadic disorder in 90% of cases. The incidence of ALS in the United States is 1.5 to 2.2 per 100.000, but varies significantly by age, sex, and race. The incidence of ALS generally increases with age and peaks during the seventh decade of life. There is not a large number of relevant studies for reliable conclusions about the connection between sports and BMN. However, there is increasing interest in the role of contact sports (eg, American football and rugby) following the diagnosis of BMN in several high-profile professional athletes. Several case-control studies have found an increased risk of MND among people who engage in strenuous physical activity, but other studies of this type did not find this risk (association) or the association was negative. Several other studies have shown an increased risk of BMN with traumatic brain injury, while others have found no association. The risk of MND varies depending on the type of sport played. For many individual sports, no increased risk of BMN was observed, including cricket, basketball, tennis, swimming, hockey, volleyball, badminton, field hockey, sailing, rowing, diving and skiing. However, several meta-analyses have shown a 1.3 to 1.7 times higher risk of MND in athletes who suffer a head injury, compared to the general population. Experience shows that exercise can be physically and psychologically important for people with ALS. Although the results so far do not provide clear conclusions regarding physical therapy or/and exrecise regimens to maintain function and quality of life in people with ALS, we can say, for sure, that moderate exercise is not harmful. Regarding the type of exercise, moderate intensity and not very high frequency (two sessions per week), combining strength and aerobic resistance, may be the best option to see improvements in ALS patients and prevent fatigue that further impairs their quality of life.

Key words: *amyotrophic lateral sclerosis – sports – physical therapy*

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INTRODUCTION

The disease with damage to both CMN and PMN is amyotrophic lateral sclerosis (ALS), belongs to the neuromuscular and neurodegenerative diseases (deterioration or "amyotrophy" of motor neurons). It was first described in 1824 by Charles Bell, and in 1869 the French neurologist Jean-Martin-Charcot (1825-1893) established a link between the symptoms of the disease and a neurological disorder (Figure 1). The term "amyotrophic lateral sclerosis" was coined by Jean-Martin Charcot in the 1800s: "amyotrophic" refers to muscular atrophy, and "lateral sclerosis" describes the scarring or hardening of tissues in the lateral spinal cord, i.e. of the corticospina tract (Goetz 2000). Disease with damage to both central motor neuron (CMN) and peripheral motor neuron (PMN), motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS), belongs to neuromuscular and neurodegenerative diseases (degeneration or "amyotrophies" of motor neurons). In the US, ALS is named Lou Gehrig's disease, after the famous baseball player who had the disease (diagnosed in 1939) (Figure 2). Motor neuron diseases (MNDs) are a group of relatively rare, progressive and terminal neurodegenerative conditions (with amyotrophic lateral sclerosis/ALS being the most common) characterized by degeneration of upper and lower motor neurons leading to motor and extra-motor symptoms (van Es et al. 2017, Chen et al. 2022). There are 2 primary classifications of ALS: sporadic (idiopathic) and familial. Familial ALS occurs in about 5% to 10% of patients with ALS, usually due to a dominant trait. Sporadic ALS encompasses all other 90-95% patients with ALS. The affected population of sporadic ALS com-

prises approximately 67% males. In familial ALS, an almost 1:1 ratio of males to females is noted. Familial type of ALS occurs in patients in their late teens or early adulthood, and the other hand sporadic ALS usually occurs in patients in their mid-to-late fifties (80-60 years). Furthermore, the average survival from onset to death is 3-4 years (Brown & Al-Chalabi 2017, Mulder et al. 1986, Talbott et al. 2016).

Figure 1. Jean-Martin-Charcot (1825-1893)

Clinical phenotypes of ALS can be grossly classified based on the level and anatomical area of motor neuron involvement and pattern of onset. Typical, or "classical," ALS involves simultaneous CMN and PMN signs and is usually fatal within four years of onset. Muscle weakness begins in a discrete body region and advances steadily over time and space. It usually begins in any of the three main body regions (face, arm, and leg), although it rarely begins in the muscles affecting the trunk and/or respiration. Pathological burden is normally distributed between CMNs and PMNs with a possible slight skew to PMN dominance. Atypical forms of the disease are cases in which there is much longer survival, or pure CMN or PMN involvement. These atypical forms may contain instances of spastic paraplegia, autoimmune diseases, or demyelinating PMN disease (Ravits et al. 2007, Grad et al. 2017). In most cases, ALS presents as progressive muscle atrophy and weakness. The most frequent complications are respiratory failure due to weakness of the thoracic musculature, and aspiration pneumonia due to dysphagia. About 20% of patients survive for 5 years after diagnosis, and 5% for 10 years or more. Compared with women, men have a higher risk of developing sporadic onset ALS, although this risk tends to equalize with increasing age. This progressive disease unfortunately leads to death. Patients with genetic or bulbar involvement have a worse prognosis (Castro-Rodriguez et al. 2021). While there is no cure for ALS to date, recent studies have shown treatment may slow loss of function and improve quality of life, particularly when provided as part of an interdisciplinary approach to patient management (Kiernan et al. 2011). There are currently four prescription drugs approved by the Food and Drug Administration for use with people with ALS, with two drugs (riluzole and edaravone) purposed to increase survival – albeit minimally (Brown & Al-Chalabi 2017). Effective therapies for ALS are postulated to inhibit excessive motor neuron activity, decrease oxidative stress, and delay respiratory decline – the latter being the major cause of mortality. Until a cure is found, clinical care continues to involve early interventions promoting improved symptom management (Donohue et al. 2023).

Figure 2. Lou Gehrig (1903- 1941)

EPIDEMIOLOGY

ALS is the most common form of motor neuron disease, with a mean incidence of 2.8/100,000 in Europe. The incidence of ALS in the United States is 1.5 to 2.2 per 100 000 but varies markedly depending on age, sex, and race. The incidence of ALS generally increases with age and peaks during the seventh decade of life. Men have a higher incidence of ALS (1.7-2.6 per 100 000) than women (1.1-1.5 per 100 000)(10). In the United States, 6000 new patients are diagnosed with ALS each year. The prevalence of ALS is 5 - 6 per 100,000 of the US population. The highest prevalence of ALS is in whites, males, and people 60 years or older. Globally, the mean age of ALS onset is 62 years (Punjani et al. 2020, Mehta et al. 2018, Chio et al. 2013). In most cases, disease onset occurs during late adulthood, but juvenile (before 25 yr) and "young-onset" ALS cases (before 45 yr), respectively, represent about 1% and about 10% of all cases (Turner et al. 2012). According to a systematic review and meta-analysis, by Xu et al. (2020), the overall crude worldwide ALS prevalence is 4.42 per 1,00,000 population and incidence 1.59 per 1,00,000 person-years,

respectively. Furthermore in a recent systematic review incidence rang from 0.26 per 100,000 person-years in Ecuador to 23.46 per 100,000 person-years in Japan. Point prevalence range from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States (Wolfson et al. 2023).

ETIOPATHOGENESIS

ALS is characterized by progressive the UMN and LMN degeneration that affects the brainstem, cervical, thoracic, and lumbosacral regions. The cause of this neurodegenerative process in ALS is not yet understood. Although the mechanisms leading to otor neurone degeneration are incompletely understood, free radical toxicity, glutamate excitotoxicity, mitochondrial dysfunction, and intermediate filament aggregation may lead to activation enzymes that regulate cell death pathways. Cell death seems to require an interaction between the MN and surrounding support cells, and the process of cell death stimulates an inflammatory reaction. Inflammation may be linked to the etiology of ALS, or may be a secondary phenomenon that intensifies neuronal damage (Lopez-Pingarron et al. 2023). The aetiology of ALS is considered to be due to a combination of risk-genotypes that interact with environmental factors over time, accelerating the neurodegenerative cascade, but until kow few conclusieve risk factors have been established (Chen et al. 2022, Lopez-Pingarron et al. 2023). Heritability studies suggest that about 60% of ALS risk is genetically determined, and the remainder is environmental. Many of the genetic mutations linked to ALS, even those which are highly penetrant, are present for more than 50 years before disease onset. The late age of onset of ALS could indicate to a multistep process, in which genetic risk factors are penetrant only in the presence of additional environmental factors.The most common mutation linked to ALS is an intronic G4C2-repeat expansion of C9ORF72, which affects about 10% of all ALS patients (Bradley e al. 2018, Al-Chalabi & Hardiman 2013, Majounie et al. 2012). Until now, the only confirmed risk factors for ALS are male sex and increasing age, with onset most commonly between 60 and 75 years of age. Over the last decade, multiple reports have been released attempting to delineate the environmental risk factors predisposing to the development of ALS, for example, repetitive head impacts, strenuous, repetitive exercise, and traumatic brain injury, however these have often been underpowered and have not led to significant advances in the field (Majounie et al. 2012, Chapman et al. 2023, Ingre al. 2015, Niccoli et al. 2017).

PHYSICAL ACTIVITY AND AMYOTROPHIC LATERAL SCLEROSIS

The role of physical activity in the aetiology of ALS has been debated over several decades (Chapman et al. 2023). However, there are not a large number of relevant studies for reliable conclusions about the connection between sports and motor neuron disease (MND). However, there is growing interest in the role of contact sports (football/or soccer in the United States, American football and rugby) following MND diagnoses in several high-profile professional athletes (Chen et al. 2022, Walt et al. 2018, Blecher et al. 2019). Association with professional sports may be due to high strenuous physical exertion (inducing oxidative stress and glutamate excitotoxicity) and/or more frequent traumatic brain injury, although evidences are controversal (Chen et al. 2022, Harwood et al. 2009). Several case-control studies reported an increased MND risk among people who engage in strenuous physical activities, but other case-control studies reported no or inverse associations (Okamoto et al. 2009, Beghi et al. 2010, Huisman et al. 2013, Veldink et al. 2005, Pupillo et al. 2014). Furthermore, several studies have shown an increased risk of MND with traumatic brain injury, while others found no association (Chen et al. 2022, van Es et al. 2017, Beghi et al. 2010, Pupillo et al. 2012, Seals et al. 2016, Feddermann-Demont et al. 2017, Turner et al. 2010). Meta-analyses have indicated a 1.3-fold to 1.7-fold increased risk of MND in relation to a head injury (Chen et al. 2007, Wang et al. 2017, Liu et al. 2017, Gu et al. 2021). However, another meta-analysis found that the association was weaker and suggested that due to reverse causation, head-injury-associated risk of ALS has been somewhat overestimated (Watanabe & Watanabe 2017). In the systematic review Blecher et al. (2019) tesed the hypothesis that competitive sports at the highest level that involve repetitive concussive head and cervical spinal trauma result in an increased risk of ALS compared with the general population or nonsport controls. They searsced electronic databases from inception to November 22, 2017. Sixteen studies met the inclusion criteria. Sports assessed (professional or nonprofessional) included soccer (n = 5), American football (n = 2), basketball (n = 1), cycling (n = 1), marathon or triathlon (n = 1), skating (n = 1), and general sports not specified (n = 11). In conclusion of this review authors suggests that increased susceptibility to ALS is significantly and independently associated with 2 factors: professional sports and sports prone to repetitive concussive head and cervical spinal trauma. Their combination resulted in an additive effect, further increasing this association to ALS. A Swedish study among cross-country skiers showed an increased risk for elite skiers but not for recreational skiers (Fung et al. 2016). Namely, Fang et al. (2016) aimed to examine whether long distance cross-country skiers have also a higher risk of ALS and whether the increased risk was modified by skiing performance. They followed 212,246 cross-country skiers in the Swedish Vasaloppet cohort and a random selection of 508,176 general Swedes not participating in the Vasaloppet during 1989-2010. The associations between cross-country skiing as well as skiing performance (i.e., type of race, finishing time and number of races) and the consequent risk of ALS were estimated through hazard ratios derived from

Cox model. During the study, 39 cases of ALS were ascertained among the skiers. The fastest skiers (100-150% of winner time) had more than fourfold risk of ALS, as compared to skiers that finished at more than 180% of winner time. Skiers who participated more tjna four races during this period had also a higher risk than those participated only one race. When compared to the non-skiers, the fastest skiers still had a higher risk as skiers who had more than four races, but those finishing at more than 180% of winner time had a lower risk. They concluded, that long distance cross-country skiing is associated with a higher risk of ALS, but only among the best skiers; recreational skiers appear to have a largely reduced risk (Funk et al. 2016). A prospective cohort study among postmenopausal women showed that strenuous physical activities were associated with an increased risk of MND, in contrast, another cohort study in European Prospective Investigation into Cancer and Nutrition showed a slightly reduced risk of dying from ALS in those with high levels of total physical activity at enrolment (Eaglehouse et al. 2016, Gallo et al. 2016). Evidence for cumulative measures of physical activity as a risk factor for ALS has been inconclusive. However, cohort studies report a significantly higher incidence of ALS in professional football and American football players, and a slightly increased risk of ALS in collegiate athletes (Gallo et al. 2016). MND risk differed by the type of sport played. For many individual sports, Chen et al. (2022) in recent New Zealand case–control study did not observe an increase in MND risk, including cricket, basketball/netball, tennis, swimming, hockey, volleyball, badminton, lawn bowl, yachting, rowing, diving and skiing. Furthermore, a number of common sports in New Zealand were associated with elevated ORs that did not reach statistical significance, including rugby, football (soccer), running and golf. However, in this New Zealand case–control study they determined that head injury with concussion ≥3 years before diagnosis was associated with MND, with strongest associations for two, and three or more head injuries. Spine injury was not associated with MND (Chen et al. 2022). In study by Pupillo et al. (2014) from February 2008 to April 2012, 652 patients with ALS from European population-based registries (France, Ireland, Italy, United Kingdom, Serbia) and 1,166 population controls (matched for age, sex, and residency) were analyzed with aim to To assess whether physical activity is a risk factor for ALS. Overall physical activity was associated with reduced odds of having ALS as were work-related physical activity and organized sports. An inverse correlation was observed between ALS, the duration of physical activity ($p=0.0041$), and the cumulative metabolic equivalents scores, which became significant for the highest exposure. An inverse correlation between ALS and sport was found in women but not in men, and in subjects with repeated traumatic events. They concluded that physical activity is not a risk factor for ALS and may eventually be protective against the disease (Pupillo et al. 2014). The multicenter population-based case-control study by McCrate and Kaspar (2008) suggests that physical activity is not a risk factor for ALS, and may eventually be protective against the disease. An inverse correlation was found for physical activity (overall), work-related and sport-related physical activity, and organized sports. Possible mechanisms underlying the neuroprotective effects of exercise include changes in motor neuron morphology, muscle-nerve interactions, glial activation, and altered levels of gene expression of ant apoptotic proteins, scavengers of reactive oxygen species, and neurotrophic factors (McCrate & Kasper 2008). Consistent with these findings in a population-based case–control study, Longstreth et al. (1998) showed that physical activity, whether at work, during leisure time, or both, and whether during a person's lifetime or during specific decades before the reference date, was not a risk factor for developing ALS (Longstreth et al. 1998). The same results are reported by Valenti et al. (2005). Veldink et al. (2005) also found no association between physical activity and the risk of developing ALS. A meta-analysis by Hamidou et al. (2014) also found that physical activity is not a risk factor for ALS. In systematic review by Lacorte et al. (2016) aim was gathering all available evidence on the association between physical activity and the risk of ALS. Relevant literature published up to January 2015 was gathered through structured searches on Medline, The Cochrane Library, and the ISI Web of Science databases. Studies considering any type of PA as the main exposure and a diagnosis of ALS or motor neuron disease were selected. Bibliographic searches yielded 3168 records. Nineteen case control studies and 7 cohort studies met the inclusion criteria, and were included in the analysis. Evidence on cumulative measures of physical activity as a risk factor for ALS remain inconclusive. However, cohort studies report a significantly higher number of cases of ALS in professional soccer and American football players, and a slightly increased risk of ALS in varsity athletes (Lacorte et al. 2016). Jansen et al. (2017) conducted a community-based study in which they analyzed whether whether athletes who played American varsity high-school football between 1956 and 1970 have an increased risk of neurodegenerative diseases later in life. For this purpose they identified all male varsity football players between 1956 and 1970 in the public high schools of Rochester, Minnesota, and non-football-playing male varsity swimmers, wrestlers, and basketball players. Using the medical records linkage system of the Rochester Epidemiology Project, we ascertained the incidence of late-life neurodegenerative diseases: dementia, parkinsonism, and amyotrophic lateral sclerosis. They identified 296 varsity football players and 190 athletes engaging in other sports. Football players had an increased risk of medically documented head trauma, especially if they played football for more than 1 year. Compared with nonfootball athletes, football players did not have an increased risk of neurodegenerative disease overall or of the individual conditions of dementia, parkinsonism, and amyotrophic lateral sclerosis. They concluded that varsity high school football players from 1956 to 1970 did not have an increased risk

of neurodegenerative diseases compared with athletes engaged in other varsity sports (Jansen et al. 2017). A recent Mendelian randomization study suggested a positive association between physical exercise and ALS in those with a specific risk genotype. Using MR approach Julian et al. (2021) suggests a positive causal relationship between ALS and physical exercise. Exercise is likely to cause motor neuron injury only in patients with a risk-genotype. Consistent with this they have shown that ALS risk genes are activated in response to exercise. In particular, they propose that G4C2-repeat expansion of C9ORF72 predisposes to exercise-induced ALS (Julian et al. 2021).

ALS AND PHYSICAL THERAPY

In one of the first systematic reviews Dalbello-Haas et al. in 2008. systematically reviewed randomised and quasi-randomised studies of exercise for people with ALS or MND. They searched the Cochrane Neuromuscular Disease Group Trials Register, EMBASE (January 1980 to August 2007), LILACS (January 1982 to August 2007), MEDLINE (January 1966 to August 2007), Cochrane Central Register of Controlled Trials (CENTRAL), PEDro (January 1980 to August 2007), AMED (January 1985 to August 2007), HealthSTAR (January 1975 to August 2007), CINAHL (January 1982 to August 2007). Theye also searched Dissertation Abstracts, inspected the reference lists of all papers selected for review and contacted the authors with expertise in the field. Two review authors independently assessed trial quality and extracted the data. The authors of the papers were contacted to obtain information not available in the published articles. They identified only two randomised controlled trials that met inclusion criteria if the study. The first examined the effects of a twice-daily exercise program of moderate load, endurance exercise versus "usual activities" in 25 people with ALS. The second examined the effects of thrice weekly moderate load and moderate intensity resistance exercises compared to usual care (stretching exercises) in 27 people with ALS. After three months, when the results of the two trials were combined, there was a significant weighted mean improvement in the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) measure of function in the exercise compared with the control groups (3.21, 95% confidence interval 0.46 to 5.96) in favour of the exercise group. No statistically significant differences in quality of life, fatigue or muscle strength were found. Therfore they concluded that the only studies detected were too small to determine to what extent strengthening exercises for people with ALS are beneficial, or whether exercise is harmful. There is a complete lack of randomised or quasi-randomised clinical trials examining aerobic exercise in this population. Finally they emphasized that more research is needed (Dalbello-Haas et al. 2008). Five years later, the same authors updated the previous review (Dalbello-Haas & Florence 2013). They used the same Cochrane literature review method: Searched The Cochrane Neuromuscular Disease Group Specialized Register (2 July 2012), CENTRAL (2012, Issue 6 in The Cochrane Library), MEDLINE (January 1966 to June 2012), EMBASE (January 1980 to June 2012), AMED (January 1985 to June 2012), CINAHL Plus (January 1938 to June 2012), LILACS (January 1982 to June 2012), Ovid HealthSTAR (January 1975 to December 2012). They also searched ProQuest Dissertations & Theses A&I (2007 to 2012), inspected the reference lists of all papers selected for review and contacted authors with expertise in the field. Authors identified again only two randomised controlled trials that met study inclusion criteria, and found no new trials when we updated the searches in 2012, with the same conclusion (Dalbello-Haas & Florence 2013). According to Elisabetta Pupillo who led a European population-based case-control study which aimed to assess whether physical activity is a risk factor for amyotrophic lateral sclerosis (ALS), physical activity is not a risk factor for ALS and may eventually be protective against the disease (Pupillo et al. 2014). Gibbons et al. (2018) in tehir Cochrane literature review which was published in 2018. assessed the effects of pharmacological and non-pharmacological interventions for fatigue in ALS/MND. They searched the following databases on 5 September 2017: Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL Plus, and ERIC, and also searched two clinical trials registries. Authors selected randomised and quasi-randomised controlled trials of any intervention which sought to reduce fatigue for people with ALS/MND, and included studies if reduction in fatigue was a primary or secondary outcome of the trial. They included one pharmacological (modafinil) study and three non-pharmacological studies (resistance exercise, respiratory exercise, and repetitive transcranial magnetic stimulation (rTMS)), involving a total of 86 participants with ALS/MND, and they emphasized that none of the included studies were free from risk of bias. Ther conlusion were: it is impossible to draw firm conclusions about the effectiveness of interventions to improve fatigue for people with ALS/MND as there are few randomised studies, and the quality of available evidence is very low (Gibbons er al. 2018). Recent meta anlysis by Donohue et al. (2023) with objective to systematically evaluate post-exercise outcomes related to function and quality of life in people with ALS included 16 studies and seven functional outcomes which were in accordance with inlcuion criteria for the meta-analysis. Results of this study showed out of the outcomes explored, the ALSFRS-R demonstrated a favorable summary effect size and had acceptable heterogeneity and dispersion. While Functional Independence Measurement (FIM) scores demonstrated a favorable summary effect size, heterogeneity limited interpretations. Other outcomes did not demonstrate a favorable summary effect size and/or could not be reported due to few studies reporting outcomes. Authors concluded that the study provides inconclusive guidance regarding exercise regimens to maintain function and quality of life in people with ALS

due to study limitations (e.g., small sample size, high attrition rate, heterogeneity in methods and participants, etc.). Thus, experience indicates that exercise can be physically and psychologically important for people with ALS. However, although recent studies have focused on what type of exercise is most adequate for these patients, there is still no evidence about either the frequency or intensity of exercise or the extent to which it helps patients maintain functionality. This is why the patient evaluation process is very important in order to analyze the effects of the intervention being used. In this sense, it is very important to have a tool that allows studying the status and evolution of a patient with ALS. The Amyotrophic lateral sclerosis functional scale revised (ALSFRS-R) is the measure most commonly used to assess the status and progression of ALS patients. Regarding the type of exercise, moderate intensity and not very high frequency (two sessions per week), combining strength and aerobic resistance, may be the best option to see improvements in ALS patients and prevent fatigue from further worsening their quality of life (Salas Campos et al. 2010, Kato et al. 2018, Ortega-Hombrados et al. 2021).

CONCLUSION

There are not a large number of relevant studies for reliable conclusions about the connection between sports and ALS. Several case-control studies and meta-analyses reported an increased ALS risk among people who engage in strenuous physical activities, but other case-control studies and meta-analyses reported no or inverse associations. There is no evidence that physical activity in general is a risk factor for ALS. We still need more evidence for the link between hard contact sports and ALS, and in particular scientific evidence and explanations for this link. We cannot come to certain conclusions only through epidemiological case-control studies or meta-analyses. More prospective studies will be needed on a larger number of patients with this rare disease, including genetic analyzes as well as analyzes of other factors. Therapeutic physical exercise could contribute to slowing down the deterioration of the musculature of patients with ALS, thus facilitating their performance in activities of daily living, based on the significant differences shown in the short, medium and long term both in subjective perception, measured with ALSFRS-R, and functional capacities. Regarding the type of exercise, moderate intensity and not very high frequency, combining strength and aerobic resistance, may be the best option to see improvements in ALS patients and prevent fatigue from further worsening their quality of life

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Contribution of individual authors:
Osman Sinanović: concept and design of article, literature searches, writing manuscript, approval of final version. Muhamed Lepuzanović & Edin Bešlagić: comments on the concept of article, literature searches, approval of the final version.

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Correspondence:
Professor Osman Sinanović, MD, MrSc, PhD
Medical Faculty, University of Tuzla, 75000 Tuzla, Bosnia and Herzegovina
Sarajevo Medical School, Sarajevo School of Science and Technology, 71210 Sarajevo; Bosnia and Herzegovina
International Academy of Science and Arts of Bosnia and Herzegovina;
Academy of Medical Sciences of Bosnia and Herzegovina, 7100 Sarajevo; Bosnia and Herzegovina
E-mail: osman.sinanovic1@gmail.com