

Editorial

Effects of Physical Activity on Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disease characterized by the loss of upper and lower motor neurons. To date, no resolutive cure is available, and only two Food and Drug Administration-approved drugs are used to treat ALS without a resolutive outcome. In recent years, the study of the beneficial effects of physical activity on health has acquired special relevance. However, the relationship between ALS progression and physical exercise is still a hotly debated topic in medicine. Some studies have suggested higher risks to develop the disease that are associated with practicing intense physical activity, as seen in professional soccer or football players, for example. On the contrary, moderate training has been shown to exert several benefits in ALS-affected patients. Overall, more studies are needed to clarify whether physical activity is helpful or harmful for developing ALS.

Keywords: amyotrophic lateral sclerosis; physical activity; neuroprotection

Amyotrophic lateral sclerosis (ALS) cases are classified into two types: sporadic ALS (SALS) (~90–95% of ALS) and familial ALS (FALS) (~5%–10% of ALS) form. The SALS etiology is unknown; on contrary, the FALS forms are due to mutations in specific genes, such as chromosome 9 open reading frame 72 (C9ORF72), transactive response DNA binding protein 43 (TARDBP), and Cu/Zn superoxide dismutase 1 (SOD1) [1]. The latter occurs in ~20% of FALS cases [2], and over the years more than 160 mutations in SOD1 gene have been found, including G93A, A4V, H46R, and D90A.

The pathogenetic mechanism involved in motor neuron degeneration during ALS is not understood yet. However, it seems that several insults contribute to MN damage, including excitotoxicity, increased oxidative stress, neurofilament aggregation, alteration of axonal transport, protein misfolding/aggregation, and activation of microglia leading to inflammation [3–7].

A specific treatment for ALS-affected patients has not been found yet. To date, riluzole and edaravone have been approved by the Food and Drug Administration to treat ALS [8,9]. However, these drugs provide modest benefits limited to some patients.

Physical activity represents a useful means in which to improve general health [10]. It positively affects cardiovascular and neuromuscular systems by improving respiratory, heart, and circulatory function and increasing the hypertrophy and strength of muscle fibers [11,12].

The beneficial effects of physical exercise are also relevant in several pathologies, including cardiovascular and pulmonary diseases, metabolic disorders (e.g., type 2 diabetes and obesity), muscle, bone, and joint diseases, cancer, and neurodegenerative disease [13–17].

Until now, the role of physical exercise in ALS pathology has been controversial. Some epidemiological studies have suggested that people practicing intense physical activity, like professional soccer or football players, have a higher risk of developing the disease [18–21]. This could be due to hard and prolonged exercise inducing inflammation, oxidative stress, and glutamate excitotoxicity in MNs, all mechanisms involved in their degeneration. On the other hand, some evidence has shown the protective effect of mild physical exercise in ALS. Studies performed on

G93A-SOD1 transgenic mice have demonstrated that moderate running-based training increased their survival rate by delaying the onset of disease [22,23]. On the contrary, high endurance exercise seems to have detrimental, if any, effects in these animals [24]. Therefore, the intensity of training represents a crucial aspect for consideration in order to ensure the benefits of physical activity. Neuroprotective effects have also been observed in ALS mice after swimming training. This type of physical activity reduced MN loss due to the modulation of different trophic factors, such as insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) [25]. In accordance, IGF-1 and BDNF are key players of different neuronal functions in the central nervous system, including synaptic density, neurogenesis, and neuron differentiation and survival [26–28]. Other studies support the hypothesis that physical activity may also play a beneficial role in ALS patients. Ribeiro et al. [29] showed cessation of muscle cramps in three patients performing yoga therapy, which was composed of breathing and relaxation exercises. Different types of exercise training, including stretching, resistance, or concurrent training, display positive effects on the quality of life by improving muscle strength and cardiorespiratory function [30,31]. In particular, Drory et al. [32] showed that a moderate daily exercise program decreased the loss of motor function, fatigue, and pain of ALS patients after 6 months. Improvements in motor function and quality of life were also found in ALS patients performing daily stretching and resistance exercises [33]. However, the limited number of patients and the small period considered limit the ability of these studies to support the hypothesis that moderate physical exercise is beneficial for ALS patients. In accordance, Dal Bello-Haas and Florence [34], in an update of a review first published in 2008, declared that “there is a complete lack of randomised or quasi-randomised clinical trials examining aerobic exercise in ALS population”.

In conclusion, the role of physical activity during development of ALS is still a debated topic. Future studies are needed to clarify whether it is helpful or harmful for disease progression.

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References

1. Brown, R.H. Jr. Amyotrophic lateral sclerosis: recent insights from genetics and transgenic mice. *Cell* **1995**, *80*, 687–692.
2. Rosen, D.R.; Siddique, T.; Patterson, D.; Figlewicz, D.A.; Sapp, P.; Hentati, A.; Donaldson, D.; Goto, J.; O'Regan, J.P.; Deng, H.-X.; et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* **1993**, *362*, 59–62.
3. Spreux-Varoquaux, O.; Bensimon, G.; Lacomblez, L.; Salachas, F.; Pradat, P.F.; Le Forestier, N.; Marouan, A.; Dib, M.; Meininger, V. Glutamate levels in cerebrospinal fluid in amyotrophic lateral sclerosis: a reappraisal using a new HPLC method with coulometric detection in a large cohort of patients. *J. Neurol. Sci.* **2002**, *193*, 73–78.
4. De Vos, K.J.; Grierson, A.J.; Ackerley, S.; Miller, C.C. Role of axonal transport in neurodegenerative diseases. *Annu. Rev. Neurosci.* **2008**, *31*, 151–173.
5. Hirano, A.; Donnenfeld, H.; Sasaki, S.; Nakano, I. Fine structural observations of neurofilamentous changes in amyotrophic lateral sclerosis. *J. Neuropathol. Exp. Neurol.* **1984**, *43*, 461–470.
6. Halter, B.; Gonzalez de Aguilar, J.L.; Rene, F.; Petri, S.; Fricker, B.; Echaniz-Laguna, A.; Dupuis, L.; Larmet, Y.; Loeffler, J.P. Oxidative stress in skeletal muscle stimulates early expression of Rad in a mouse model of amyotrophic lateral sclerosis. *Free Radic. Biol. Med.* **2010**, *48*, 915–923.
7. Blokhuis, A.M.; Groen, E.J.; Koppers, M.; van den Berg, L.H.; Pasterkamp, R.J. Protein aggregation in amyotrophic lateral sclerosis. *Acta Neuropathol.* **2013**, *125*, 777–794.
8. Petrov, D.; Mansfield, C.; Moussy, A.; Hermine, O. ALS clinical trials review: 20 years of failure. are we any closer to registering a new treatment? *Front. Aging Neurosci.* **2017**, *9*, 68.
9. Sawada, H. Clinical efficacy of edaravone for the treatment of amyotrophic lateral sclerosis. *Expert Opin. Pharmacother.* **2017**, *18*, 735–738.

10. Castrogiovanni, P.; Di Rosa, M.; Ravalli, S.; Castorina, A.; Guglielmino, C.; Imbesi, R.; Vecchio, M.; Drago, F.; Szychlinska, M.A.; Musumeci, G. Moderate Physical Activity as a Prevention Method for Knee Osteoarthritis and the Role of Synoviocytes as Biological Key. *Int. J. Mol. Sci.* **2019** *20*, pii: E511.
11. Wu, N.; Bredin, S.; Guan, Y.; Dickinson, K.; Kim, D.D.; Chua, Z.; Kaufman, K.; Warburton, D. Cardiovascular Health Benefits of Exercise Training in Persons Living with Type 1 Diabetes: A Systematic Review and Meta-Analysis. *J. clin. Med.* **2019** *8*, 253.
12. Szychlinska, M.A.; Castrogiovanni, P.; Trovato, F.M.; Nsir, H.; Zarrouk, M.; Lo Furno, D.; Di Rosa, M.; Imbesi, R.; Musumeci, G. Physical activity and Mediterranean diet based on olive tree phenolic compounds from two different geographical areas have protective effects on early osteoarthritis, muscle atrophy and hepatic steatosis. *Eur. J. Nutr.* **2019** *58*, 565–581.
13. Castrogiovanni, P.; Trovato, F.M.; Szychlinska, M.A.; Nsir, H.; Imbesi, R.; Musumeci, G. The importance of physical activity in osteoporosis. From the molecular pathways to the clinical evidence. *Histol. Histopathol.* **2016** *31*, 1183–1194.
14. Musumeci, G. Effects of exercise on physical limitations and fatigue in rheumatic diseases. *World J. Orthop.* **2015** *6*, 762–769.
15. Pedersen, B.K.; Saltin, B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J. Med. Sci. Sports* **2006** *16*, 3–63.
16. Warburton, D.E.; Nicol, C.W.; Bredin, S.S. Health benefits of physical activity: the evidence. *CMAJ* **2006a** *174*, 801–809.
17. Warburton, D.E.; Nicol, C.W.; Bredin, S.S. Prescribing exercise as preventive therapy. *CMAJ* **2006b** *174*, 961–974.
18. Strickland, D.; Smith, S.A.; Dolliff, G.; Goldman, L.; Roelofs, R.I. Physical activity, trauma, and ALS: a case-control study. *Acta Neurol. Scand.* **1996** *94*, 45–50.
19. Gotkine, M.; Friedlander, Y.; Hochner, H. Triathletes are over-represented in a population of patients with ALS. *Amyotroph. Lateral. Scler. Frontotemporal. Degener.* **2014** *15*, 534–536.
20. Chio, A.; Benzi, G.; Dossena, M.; Mutani, R.; Mora, G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* **2005** *128*, 472–476.
21. Lehman, E.J.; Hein, M.J.; Baron, S.L.; Gersic, C.M. Neurodegenerative causes of death among retired National Football League players. *Neurol* **2012** *79*, 1970–1974.
22. Veldink, J.H.; Bar, P.R.; Joosten, E.A.; Otten, M.; Wokke, J.H.; van den Berg, L.H. Sexual differences in onset of disease and response to exercise in a transgenic model of ALS. *Neuromuscul Disord* **2003** *13*, 737–743.
23. Liebetanz, D.; Hagemann, K.; von Lewinski, F.; Kahler, E.; Paulus, W. Extensive exercise is not harmful in amyotrophic lateral sclerosis. *Eur. J. Neurosci.* **2004** *20*, 3115–3120.
24. Mahoney, D.J.; Rodriguez, C.; Devries, M.; Yasuda, N.; Tarnopolsky, M.A. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. *Muscle Nerve* **2004** *29*, 656–662.
25. Deforges, S.; Branchu, J.; Biondi, O.; Grondard, C.; Pariset, C.; Lecolle, S.; Lopes, P.; Vidal, P.P.; Chanoine, C.; Charbonnier, F. Motoneuron survival is promoted by specific exercise in a mouse model of amyotrophic lateral sclerosis. *J. Physiol.* **2009** *587*, 3561–3572.
26. Brooker, G.J.; Kalloniatis, M.; Russo, V.C.; Murphy, M.; Werther, G.A.; Bartlett, P.F. Endogenous IGF-1 regulates the neuronal differentiation of adult stem cells. *J. Neurosci. Res.* **2000** *59*, 332–341.
27. Tong, L.; Shen, H.; Perreau, V.M.; Balazs, R.; Cotman, C.W. Effects of exercise on gene-expression profile in the rat hippocampus. *Neurobiol. Dis.* **2001** *8*, 1046–1056.
28. Aleman, A.; Torres-Aleman, I. Circulating insulin-like growth factor I and cognitive function: Neuromodulation throughout the lifespan. *Prog. Neurobiol.* **2009** *89*, 256–265.
29. Ribeiro, S. Iyengar yoga therapy as an intervention for cramp management in individuals with amyotrophic lateral sclerosis: three case reports. *J. Altern. Complement. Med.* **2014** *20*, 322–326.
30. Lunetta, C.; Lizio, A.; Sansone, V.A.; Cellotto, N.M.; Maestri, E.; Bettinelli, M.; Gatti, V.; Melazzini, M.G.; Meola, G.; Corbo, M. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *J. Neurol.* **2016** *263*, 52–60.
31. Kato, N.; Hashida, G.; Konaka, K. Effect of muscle strengthening exercise and time since onset in patients with amyotrophic lateral sclerosis: a 2-patient case series study. *Medicine* **2018** *97*, e11145.
32. Drory, V.E.; Goltsman, E.; Reznik, J.G.; Mosek, A.; Korczyn, A.D. The value of muscle exercise in patients with amyotrophic lateral sclerosis. *J. Neurol. Sci.* **2001** *191*, 133–137.

33. Dal Bello-Haas, V.; Florence, J.M. Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database Syst. Rev.* **2013** *5*, CD005229.
34. Bello-Haas, V.D.; Florence, J.M.; Kloos, A.D.; Scheirbecker, J.; Lopate, G.; Hayes, S.M.; Pioro, E.P.; Mitumoto, H. A randomized controlled trial of resistance exercise in individuals with ALS. *Neurology* **2007**, *68*, 2003–2007.



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