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# Sport and risk of amyotrophic lateral sclerosis

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SUMMARY

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting motor neurons. Symptoms of the disease include progressive weakness and atrophy of muscles and increasing respiratory failure. The etiology of the disease is not completely unknown. Data from the literature suggest that sport can be a risk factor for ALS through vigorous physical activity, trauma or micro trauma associated with it, and the acceptance by athletes toxic substances. Research on this topic conducted in patients with ALS are not clear, but some of them point to the importance of vigorous physical activity and traumatic factors in causing

disease. The above issues require further research. The aim of the work was a review of the literature concerning sports and risk of ALS.

Keywords: amyotrophic lateral sclerosis, neurodegeneration, physical injury, sport

## INTRODUCTION AND PURPOSE OF WORK

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting motor neurons, leading to severe disability and death from ventilatory failure. The diagnosis of ALS is based on a history of progressive weakness coupled with examination findings of upper and lower motor dysfunction. No diagnostic test is yet available, but electromyography and genetic tests can support the diagnosis. The etiopathogenesis of the disease is not clear. No environmental risk factors are proved to be causative, but many have been proposed [1]. It was reported clusters of ALS in professional football players in Italy and American football players in the USA [2,3]. Lists the following factors that could cause ALS in athletes: vigorous physical activity, football-specific trauma and micro trauma, illegal toxic substances [2]. The results of studies on the effects of vigorous physical activity of developing ALS are ambiguous. Some studies show that vigorous physical activity can lead to a higher incidence of the disease, but other studies have not confirmed this fact. The aim of the work was a review of the literature concerning sport and risk of ALS.

## DESCRIPTION OF KNOWLEDGE

### Hypothetical mechanisms of ALS caused by vigorous physical activity

A growing interest in the role of vigorous physical activity in the development of motor neuron disease has followed reports of a higher incidence of the disease in professional sports people. It is also supported by hypotheses concerning the genetic and cellular mechanisms of this disease. However, evidence from epidemiological studies remains conflicting [4].

Ferraiuolo et al. [5] investigated the transcriptional adaptive response of motoneurons and muscles to voluntary exercise. The results showed that motoneurons respond to physical

activity by activating a complex transcriptional plan, with changes involved in neurotrophic factor signalling, electrophysiological changes and synaptic reorganization. The authors revealed that tissues show transcriptional changes involved in the growth and reinforcement of the neuromuscular junction. This study indicates that the neuromuscular system represents significant structural and functional alterations. The authors concluded that understanding the response of the cells during exercise has potentially important implications for human neuromuscular disease, including ALS, by highlighting candidate genes pivotal for the balance between the physiology and the pathology of the neuromuscular system in terms of the stress response to physical exercise. It is known that glial cell line-derived neurotrophic factor (GDNF) is produced by skeletal muscle and influences peripheral motor neurons. Elevated expression of GDNF in skeletal muscle leads to hyperinnervation of neuromuscular junctions. Studies have demonstrated that altered physical activity causes changes in the neuromuscular junction. The altered production of GDNF may be responsible for activity-dependent remodeling of the neuromuscular junction and may play a role in recovery from injury and disease [6].

Data from the literature showed different effects of non-muscle-damaging exercise and muscle-damaging exercise on redox homeostasis. Non-muscle-damaging exercise induces alterations in redox homeostasis that last a few hours post exercise, whereas muscle-damaging exercise causes alterations in redox homeostasis that may persist for and/or appear several days post exercise [7].

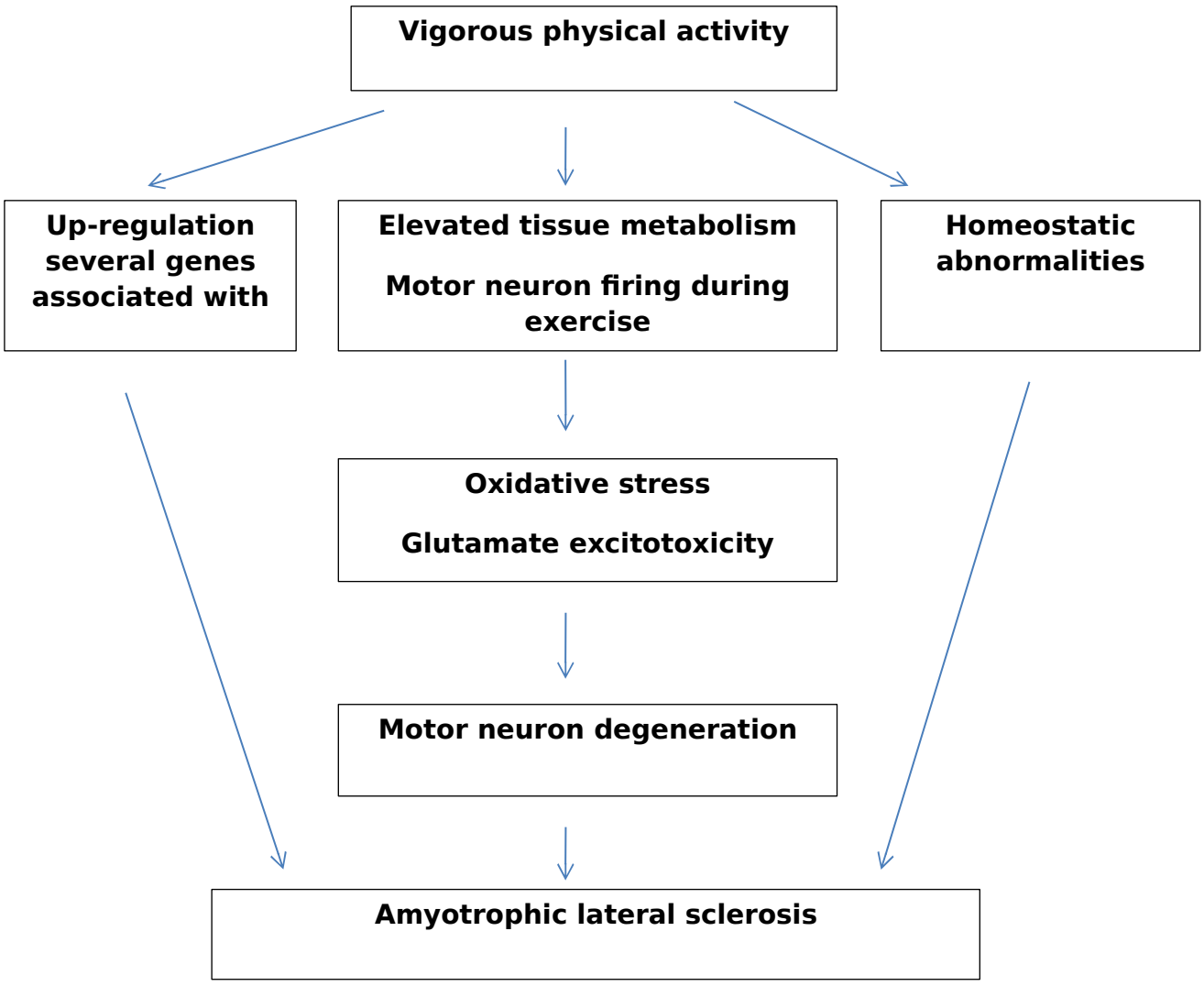
Vigorous exercise can thus cause structural and metabolic changes in skeletal muscle, including those with epigenetic relevance like DNA methylation (8).

According to Dupuis et al. [9] ALS is associated with several defects in energy metabolism, including weight loss, hypermetabolism, and hyperlipidaemia. These abnormalities correlate with clinical parameters of the disease and supports a negative contribution of defective energy metabolism to the overall pathogenic process.

Data from the literature indicate a relation between vigorous physical activity and ALS. Physical activity itself is unlikely to cause ALS, but could it modify the effects of other etiologic factors such as neurotoxins. Vigorous physical activity could potentiate the effect of a toxin to motor neurons by any of several mechanisms, especially if the toxin's effects were

mediated through excitation. Exercise could alter the extent of exposure or could influence the distribution, metabolism or potency of an excitotoxin [10].

Fig. 1. Hypothetical mechanisms of ALS caused by vigorous physical activity [5-7,9,10].



**Physical activity and risk of amyotrophic lateral sclerosis**

Data from the literature on vigorous physical activity as a risk factor for ALS are divergent.

Chio et al. [2] studied a cohort of 7325 male professional football players from the Italian First or Second Division in the period 1970-2001, and calculated standardized morbidity ratios (SMRs). The SMR was significantly increased for an ALS onset before 49 years, but not for older subjects. A significant increase of the SMR was found in the periods 1980-1989 and 1990-2001. The authors found a dose-response relationship between the duration of professional football activity and the risk of ALS and concluded that playing professional football is a strong risk factor for ALS.

Lehman et al. [3] analyzed the ALS among a cohort of professional football players and observed that neurodegenerative mortality was increased. Of the neurodegenerative causes, results were elevated for ALS. Additionally, higher neurodegenerative mortality was observed among players in speed positions compared with players in nonspeed positions. The authors concluded that the neurodegenerative mortality of this cohort is 3 times higher than that of the general population. These results are consistent with other studies that suggest an increased risk of neurodegenerative disease, including ALS, among football players.

Okamoto et al. [11] examined the associations between lifestyle factors and the risk of ALS. The study comprised 183 ALS patients and age-matched controls. The information on lifestyle factors was obtained through a questionnaire. The authors observed that vigorous physical activity, self-reported stress, a type A behavior pattern, and less frequent intakes of green-yellow vegetables were significantly associated with increased risk of ALS. These data suggested that imbalances between excessive productions of oxidants as patient-specific factors and a diminished or missing antioxidant defense system in motor neurons may increase the risk of ALS.

Gotkine et al. [12] identified patients reporting regular participation in triathlons (ALS-T) and compared clinical and demographic data to other patients with ALS. The authors

concluded that vigorous exercise itself may be related to a predominance of bulbar-onset of ALS patients, irrespective of head and neck trauma.

Harwood et al. [13] conducted study to examine the association between physical activity and ALS. The authors observed a positive associations with the strongest associations for those reporting higher levels of exercise-related physical activity throughout adulthood. However, the results did not support an earlier age of onset of ALS with greater physical activity participation.

According Chio et al. [14] prospective extension of the Italian soccer players cohort survey confirms the highly significant risk of developing ALS, the young age of onset, the dose-effect risk and a predilection for midfielders. However, the absence of ALS cases in professional road cyclists and basketball players indicates that ALS is not related to physical activity per se.

Feddermann-Demont et al. [15] examined prevalence of potential sports-associated risk factors in Swiss ALS patients. The authors retrospectively studied exposure to extrinsic factors in ALS patients in the presymptomatic stage. Metabolic equivalents (METs) were calculated and the association of physical activity, drug intake, head trauma and participation in specific sports (football, ice hockey) with age of symptom-onset was evaluated. The results from their study showed that ninety-five percent of patients were physically active before symptom-onset of the disease. There was no correlation between vigorous physical activity and age of symptom-onset. There was an association between a history of head/neck injuries and a younger age of symptom-onset. In former football and ice hockey players the rate of vigorous physical activities was increased, whereas frequency of head injuries and analgesis intake were not different compared to other patients with ALS. The authors concluded that the only extrinsic risk factor associated with accelerated neurodegeneration in ALS was history of head injuries. Moreover, there was no evidence for extrinsic factors predisposing former football and ice hockey players to ALS. According to Feddermann-Demont et al. not increased physical activity per se, but other unknown environmental factors and/or genetic factor or lifestyle-promoting physical fitness increases susceptibility of ALS.

Huisman et al. [16] determined the relation between physical activity and risk of sporadic ALS in 636 sporadic ALS patients and 2166 controls, both population based,

completed a questionnaire on lifetime history of occupations, sports and hobbies. The authors observed that ALS patients had significantly higher levels of leisure time physical activity compared with controls. No significant difference was found between patients and controls in the level of vigorous physical activities, including marathons and triathlons, or in occupational activity. The authors concluded that the lack of association with occupational physical activity and the absence of a dose-response relationship strengthen the hypothesis that not increased physical activity per se but rather a genetic profile or lifestyle promoting physical fitness increases ALS susceptibility.

Veldink et al. [17] assessed whether lifetime physical activity during work and leisure time is associated with an increased risk of developing ALS and determined the association between physical activity and duration or age at onset of disease. No significant association with occupational or leisure time physical activity was found. Higher leisure time activities were associated with an earlier age at onset. The authors concluded that there is no association between physical activity and the risk of developing ALS.

Yu et al. [18] assessed information regarding residence history, occupational history, smoking, physical activity, and other factors in ALS patients. The authors revealed that smoking, occupational exposures to metals, dust/fibers/fumes/gas and radiation, and physical activity were not associated with ALS when comparing the randomly selected ALS patients to the control subjects.

Valenti et al. [19] observed that neither the practice of competitive sports nor sports-related traumas were found to be associated with an increased risk of ALS. The practice of physical activities or sports is not per se a risk factor for ALS. However, the results excluded sports-related micro traumas as etiopathogenic factors in the natural history of ALS.

Gallo et al. [20] investigated association between physical activity and risk of death from ALS. Total physical activity was weakly inversely associated with ALS mortality with a borderline statistically significant trend across categories, with those physically active being 33% less likely to die from ALS compared to those inactive. Anthropometric measures, sex, and age did not modify the association with Cambridge Physical Activity Index. It was a first prospective cohort study on ALS and physical activity.

Pupillo et al. [21] examined 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. An inverse correlation between ALS and sport was found in women but not in men, and in subjects with repeated traumatic events. The authors concluded that physical activity is not a risk factor for ALS and may eventually be protective against the disease.

**Physical injuries and amyotrophic lateral sclerosis**

It has been suggested that ALS may also be associated with injuries during different sports. It is hypothesized that head trauma can cause neurodegeneration in the inflammatory mechanism, glutamate excitotoxicity and / or oxidative stress [22,23]. The present work is discussing the effect of injury to the formation of the disease.

Strickland et al. [24] analyzed the association of trauma and physical activity with ALS. The authors found statistically significant differences between ALS cases and controls. These included severe head, neck and back injury, the frequency of sweating in work, or leisure activity, and earning a school letter. Possible explanations include trauma and vigorous exercise precipitating ALS; trauma as an early sign of disease; or a third factor associated with ALS predisposing to injury. Severe head, neck, and back injury and frequency of sweating both in work and leisure activity showed a strong association with ALS.

Pupillo et al. (25) assessed the association between ALS and previous traumatic events, age of trauma, and site of injury. A population-based case-control study was performed in five European countries. Five hundred and seventy-five ALS patients and 1150 controls were investigated. A history of head injuries was associated with an almost three-fold increased risk of ALS. The risk was almost two-fold when trauma occurred at age 35-54 years. The authors concluded that traumatic events leading to functional disability or confined to the head are risk factors for ALS.

Chen et al. [26] examined the relationship between head injury and injuries at other body sites and risk of ALS. The authors revealed a statistically significant ALS risk elevation for participants with more than one head injury or with head injury during the past 10 years.

For participants with multiple head injuries in the past 10 years, the risk elevation was more than 11 fold. According to authors head injury may increase the risk of ALS, however physical injuries of other body parts were not related to risk of this disease. The authors suggested that it cannot be excluded that the preclinical symptoms of ALS might have predisposed patients to a higher risk of physical injuries.

Seals et al. [27] conducted study in Denmark to assess whether trauma is associated with a higher risk of ALS. Data from the study revealed that physical trauma at earlier ages is associated with risk of ALS. A first trauma before age 55 years was associated with ALS, whereas first traumas at older ages were not. There was an association with the combination of head and other traumas specifically, even after excluding traumas that occurred during the 5 years before ALS diagnosis. The authors observed that ALS patients whose first trauma occurred at younger ages had longer periods between that trauma and diagnosis of ALS. According to authors traumas experienced early in life may be associated with ALS because of a long latency period between exposure and outcome.

Peters et al. [28] examined whether severe head injury, subtypes of head injury, or repeated head injuries are associated with ALS risk based on the Swedish population and health registers. Results showed that there was an association of ALS risk with severe head injury ≤ 1 year before diagnosis. No association was observed for severe head injury > 3 years before ALS diagnosis, nor was ALS associated with subtypes of head injury or repeated injuries occurring > 3 years before diagnosis. The authors concluded that the findings from the Swedish registers provide no strong support for an etiological relationship between severe head injury in adulthood and risk of ALS.

## SUMMARY

ALS is a progressive neurodegenerative disease. The etiology of the disease is not completely understood. It is believed that various environmental factors may play a role in getting sick. It is suggested that the sport can be a risk factor for ALS by vigorous physical activity, trauma or micro injury associated with it or receipt by athletes toxic substances. The hypothetical mechanism of damage to motor neurons in ALS due to vigorous physical activity includes elevated tissue metabolism, motor neuron firing during exercise, which leads to oxidative

stress and glutamate toxicity, and also homeostatic disturbances and dysregulation of genes associated with ALS. Data from the literature on sport as a risk factor for ALS, however, are divergent. The above issues require further research.

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