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Review Article

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The Role of Omega-3 in Amyotrophic Lateral Sclerosis: A Systematic Review

Jéssica Cristina Lino da Silva[1], Natália Vilela Silva Daniel[2], Simone Rossignolo[3], Luciana Pietro[4*]

[1]Nutrition student at Paulista University UNIP, Campinas, São Paulo/SP, Brazil; Adress: Serra da Fartura, nº 51, Jardim São Fernando, Campinas-SP. CEP: 13100-360
[2]Nutritionist, Professor of the Nutrition course at Paulista University UNIP, Campinas, São Paulo/SP, Brazil; Adress: Av. Comendador Enzo Ferrari, 280 - Swift, Campinas - SP, 13045-770
[3]Nurse, Doctor, Professor of the Nursing and Medicine Course at Paulista University UNIP, Campinas, São Paulo/SP, Brazil; Address: Av. Comendador Enzo Ferrari, 280 - Swift, Campinas - SP, 13045-770
[4]Biologist, Phd, Professor of the Nutrition and Medicine Course of the Paulista University UNIP Campinas, São Paulo/SP, Brazil; Address: Av. Comendador Enzo Ferrari, 280 - Swift, Campinas - SP, 13045-770

Abstract

Introduction: Amyotrophic Lateral Sclerosis (ALS) is part of the group of neuronal motor diseases, characterized as neurodegenerative by the progressive degeneration of upper and lower motor neurons, leading to muscle atrophy, fasciculation and weakness, and consequent death from respiratory failure. Its etiology is not well understood, and several factors are taken into account, such as the causes of the disease, with impairment of the individual's nutritional status, dysphagia, loss of appetite, and hypermetabolism, causing an increased need for therapy and an even more complex nutritional intake Omega 3, is a long-chain polyunsaturated fatty acid, which has protective and beneficial effects in relation to neurodegenerative diseases, being considered an important anti-inflammatory agent by acting as an antioxidant in the fight against oxidative stress of neuronal cells, through mechanisms such as excitotoxicity, neuroinflammation, and activation of anti-apoptotic pathways that are relevant processes in the pathophysiology of ALS.

Objectives: To systematically review the role of Omega 3 supplementation in Amyotrophic Lateral Sclerosis.

Methodology: A systematic review was carried out in the scientific bases: Pubmed, ScienceDirect, Lilacs, Scielo and Medline, in English, Portuguese, addressing the themes: neurodegenerative diseases, amyotrophic lateral sclerosis and omega 3.

Results: All studies were carried out in humans, before the usual dose of omega 3 in the diet, observing how the polyunsaturated fatty acid acts in Amyotrophic Lateral Sclerosis. Of the total number of studies found, 5 demonstrated the efficiency of omega 3 in the neuroprotective effect, 2 did not observe efficiency and 1 was not conclusive.

Conclusion: It is concluded with the systematic review, that omega 3 contributes in a dietary way, easing the symptoms and/or the progression of the disease. However, more clinical studies directly aimed at this intervention must be performed to support the results found.

***Corresponding author:** Luciana Pietro, Av. Comendador Enzo Ferrari, 280 - Swift, Campinas - SP, 13045-770; Phone number: 55 (19) 99684-3274; E-mail: lucianapietro1@gmail.com

Co-author(s) emails: jeehcriss@hotmail.com (JCLdS); natalia.daniel@docente.unip.br (NVSD); simone.rossignolo@docente.unip.br (SR)

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Keywords

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is a disease of the motor neuron, being considered the most common form of progressive motor neuron disease and undoubtedly the most neurodegenerative [1]. The disease is associated with the loss of motor neurons in the spinal cord, brainstem and motor cortex, resulting in significant impairment leading to paralysis and death [2].

ALS is characterized by progressive paralysis and respiratory failure, which can lead to death within 3 to 5 years after its onset. Currently, the prevalence of ALS is 5 to 10 people per 100,000 inhabitants, with higher prevalence in the Western Pacific, Guam Island and Japan. In Europe and the United States, those most affected by the disease are males[1]. Most ALS cases are sporadic, with familial cases accounting for only about 10% [3].

With the evolution and diagnosis of the disease, there is a change in the individual's daily life, which at the same time has a negative impact, causing the loss of autonomy and the need for greater attention and comprehensive assistance to carry out day-to-day activities [4].

The etiology of ALS is not fully understood, however, the excitotoxicity of the neurotransmitter glutamate, changes in immunity, deficiency of neurotrophic factors, physical trauma, persistent viral infections and even environmental factors have been suggested as possible causes of the disease [5].

Glutamate plays an extremely important role in the brain, being the main excitatory neurotransmitter in the central nervous system (CNS) and being present in greater abundance in brain functions such as memory, brain development and cell communication. However, studies show that its gradual increase

in the synaptic cleft can lead to neurotoxicity in target neurons, characterizing itself as a strong agent in the development of neurodegenerative diseases such as ALS [6-7].

During the course of the disease, the nutritional status declines, and it is often inadequately treated. According to SALVIONI et al. [5], the disease affects the patients' bulbar muscles in the first place, resulting in long-term malnutrition.

According to KELLOGG et al. [8], there is evidence that increased energy intake and a higher body mass index, with a BMI of 30-35 kg/m², can delay the progression of ALS and change the clinical course of the disease. However, maintaining an adequate nutritional status in this population is extremely difficult, due to dysphagia, increased eating time secondary to weakness of the masticatory muscles, and anxiety related to fear of choking. On average, ALS patients consume about 15% less calories than recommended.

Nutritional recommendations directed at ALS aim to meet nutritional needs for all stages of disease progression, to minimize protein catabolism, ensuring oral feeding and the need for early nutritional support [5].

Generally, a diet with greater fractionation, high caloric content, rich in proteins, norm lipidic, with an adequate water supply, consistency and ideal temperature against dysphagia, are characteristics of diet-oriented treatment. Most of the time, the disease is already so invasive that its progression is rapid, making it difficult for the patient to feed orally. At this point, a decision must be made whether enteral nutrition is an acceptable intervention, given the prognosis for quality of life [8].

Currently there is no treatment that cures ALS, and many substances have already been tested, but did not obtain a promising result. In the case of pharmacological treatment, its main objective is to prolong and improve quality of life for patients, thus the best treatment is a combination of neuroprotective agents, symptomatic agents, nutritional therapy and ventilatory support [9].

Omega 3

The polyunsaturated fatty acid of the omega 3 type is characterized as long-chain because it is composed of 14 to 22 carbon atoms, it is called polyunsaturated because it has more than one double bond and is called omega 3 because it contains the first double bond on carbon 3, from the methyl radical. It is considered a functional component, acting in the body in numerous ways, such as reducing the risk of cardiovascular diseases, in addition to playing an important role in inflammatory processes [10].

Omega 3 fatty acids will include long chain alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [11].

Studies report that EPA is more related to clinical trials in mood disorders, while DHA is related to the treatment of neurodegenerative diseases, with omega 3 present in the brain being quantitatively the most important, since it has exclusive and indispensable roles in membranes neuronal [12].

The omega 3 fatty acid is responsible for the greater body energy reserve in children and newborns, in addition to everything else it is important and essential in neural and visual development, growth and maintenance of health itself [10]. A study with rodents showed that due to the anti-inflammatory properties and antioxidants found in fatty acids, there is a direct aid in the neuroprotective properties, since its deficiency increases the vulnerability of the brain, leading to it being an important factor for neuropathological diseases [13].

According to SANTOS [11], several epidemiological and experimental studies also indicate that omega 3 has a preventive or treatment role in depressive disorders, reporting that an omega 3 deficiency can lead to altered neuronal function and impaired inflammatory state, since lipids are essential for the structure of the brain, acting in the normality of its function, while the phospholipids composed of fatty acids play an important role in the translation of nervous signals, in the integrity of the cell membrane and in its fluidity [10].

In a study, VALENZUELA et al. [14] reported that the brain is sensitive to oxidative damage and that several tests with clinical trials in neurodegenerative diseases showed the efficiency of omega 3 in the prevention and/or treatment of these diseases, having a preventive effect on the brain caused by oxidative stress. Even though DHA is a target of oxidative damage in the cell, its pre-administration promotes antioxidant effects [15].

According to APPOLINÁRIO et al. [16], neurodegenerative diseases are associated with lipid peroxidation, which results in products that may be capable of modifying molecules, leading to the belief that these changes may have an influence on the appearance of neurodegenerative diseases.

It is important to emphasize that the protective effects of EPA and DHA can happen through many mechanisms, excitotoxicity and neuroinflammation, activation of anti-apoptotic pathways, processes that are relevant in the pathophysiology of ALS. The lipid abnormality is related to the disease, where hyperlipidemia can be a feature of ALS, in addition, a high fat diet in transgenic mice partially reversed the expression of muscle degenerative markers, motor retardation and neuron death and also extended the lifetime by 20% [2].

Amyotrophic Lateral Sclerosis is a neurodegenerative disease and is considered devastating. The disease settles in the body and spreads silently, where it ends up being very difficult to find it early to establish the best possible care. Although Lateral Sclerosis is not a disease that affects a large number of individuals, it is extremely important that they pay attention and quality of life to those who suffer so much. The disease currently does not have a cure and there are few effective pharmacological therapies that bring any proven benefit in delaying it.

In view of this, a multidisciplinary team, including nutrition with the work of nutritional therapy and studies that can add to nutritional components, which come to benefit in relation to the disease, is extremely important for the individual's improvement care, so that they have maximum comfort, acting on the improvement or even a significant progression of the disease, in addition to its prevention. For this, the administration of omega 3 could act by helping to model neuroinflammation, oxidative stress and excitotoxicity, mechanisms that have been associated with Amyotrophic Lateral Sclerosis.

Therefore, considering this justification, the present study aims to verify the role of Omega 3 in Amyotrophic Lateral Sclerosis, through a systematic review, demonstrating how nutritional therapy with omega 3 acts in Amyotrophic Lateral Sclerosis.

Methodology

It was carried out through a systematic review, the search for original articles in the languages: English and Portuguese, aiming to establish possible effects of the benefits of Omega 3 in the prevention of Amyotrophic Lateral Sclerosis. The scientific bases used were: Science Direct, Pubmed, Medline, Scielo and Lilacs, as well as scientific journals and journals available in electronic format.

The descriptors used were: "Nutritional Therapy in Amyotrophic Lateral Sclerosis"; "The Benefits of Omega 3"; "Neurodegenerative Diseases"; "Omega 3 and Amyotrophic Lateral Sclerosis"; "Omega 3 and Neurodegenerative Diseases"; "Amyotrophic lateral sclerosis"; "Diet and Amyotrophic Lateral Sclerosis"; "Food intake and Amyotrophic Lateral Sclerosis".

The inclusion criteria for carrying out the systematic review was initially the search for articles according to the titles and abstracts presented, prioritizing human studies and the dosage of omega 3 in the usual diet. After an electronic search, the most recent publications were prioritized, however, the search was expanded in order to investigate and obtain the largest possible number of publications.

Research unrelated to the topic, literature reviews, and animal studies were excluded. For each selected study, a critical analysis was performed in order to assess the validity of the results obtained and the possibility of their conclusions being based on similar data.

Results

Table 1 presents the articles selected for the present study, describing author, year, location, case and control samples, usual dosage in the diet of total fat (g), polyunsaturated fatty acids (g), p-value, duration, type of study and results found in neuroprotection.

Table 1: Follow-up of studies in humans, relating the usual dose of Omega 3 in the diet and Amyotrophic Lateral Sclerosis.

Autor, Ano e Local	Samples	Total fat (g)	Polyunsaturated (g)	*P***	Duration and type of study	Results in neuroprotection
Ahmed et al, 2016 (Australia)[17]	143 cases 25 controls	82g	10,5g	*P*>0,05	3 months FFQ	NC
Pupillo et al, 2017 (Italy)[18]	212 cases 212 controls	85,2g	7,4g	*P<0,05*	4 years FFQ	Positive effect
Veldink et al, 2007 (Netherlands)[19]	352 cases 220 controls	135,2g	25,5g	*P*<0,05	1 year FFQ	Positive effect
Okamoto et at, 2007 (Japan)[20]	153 cases NR	44,9g	13,1g	*P*<0,05	4 years FFQ	Positive effect
Fitzgerald et al, 2014 (USA)[21]	995 cases NR	NR	1,4-1,85g	*P*<0,05	8 years FFQ	Positive effect
Nieves et al, 2016 (USA)[22]	302 cases NR	72g	1,1-1,6g	*P*<0,05	5 years FFQ	Positive effect
et al 2000 (USA)[23]	180 casos 174 controls	42,2g	8g	*P*>0,05	4 years FFQ	Negative effect
Huisman et al, 2015 (Netherlands)[24]	674 cases 2.093 controls	10,33g	1,02g	*P*>0,05	5 yeas FFQ	Negative effect

* NR= Not reported. *NC= Not conclusive. *FFQ= Food Frequency Questionnaire.

According to studies by Ahmed et al. [17], carried out in Sydney, with data collected from 143 patients over a period of three months, of which 62 were diagnosed with ALS (Amyotrophic Lateral Sclerosis), 21 with ALS-FTD (related to Fronto-Temporal Dementia), 12 with ALS-Plus (insufficient cognitive and behavioral alterations to meet the diagnostic criteria for detection of ALS-FTD), 56 with bvFTD (behavioral variant frontotemporal dementia) and, finally, 25 healthy controls, which had a total consumption of 82g of fat and 10.5g of polyunsaturated fatty acids, it was found that the caloric intake of food was not considerably different between the groups, however, the intake of macronutrients in the group diagnosed with FTD showed a higher consumption of CHO and sugars.

In patients diagnosed with ALS and the bv FTD group, an increase in fat intake was observed when compared to the group of healthy patients (controls). However, there was no conclusive result on increased fat intake related to the risk of developing ALS.

Another study was by Pupillo et al. [18] carried out over a period of 4 years in Italy, with 424 patients being followed up, 212 divided into definite, probable or possible ALS (according to the El Escorial diagnostic classification), and 212 controls, where specific combinations of foods and nutrients that could be taken as risk factors or protective factors in the development of ALS were verified with a habitual dietary intake of 85.2g of total fat and 7.4g of polyunsaturated fat.

As a result, the group of patients diagnosed with ALS had a lower BMI than the control group, and it was possible to verify a relevant reduction in the risk of ALS with the consumption of coffee, tea, whole grain bread, raw vegetables and citrus fruits. In addition, a high-risk predisposition for the development of ALS associated with the consumption of beef, pork and processed meat was noted. Another important association was observed in the intake of vegetable fat, total folate and vitamin E, thus demonstrating the beneficial effect of these compounds in a possible prevention of ALS.

In addition, Veldink et al. [19] carried out another study with 135 patients diagnosed with ALS, where they applied questionnaires associated with food. The analysis of the results confirmed the association of PUFA's intake (135.2g of total fat and 25.5g of polyunsaturated fatty acids) and vitamin E with beneficial effects of two compounds in the prevention of ALS.

It was observed that total cholesterol intake was more expressive in patients with ALS, although without significance. For greater coverage of the study, the pre-morbid intake of dietary supplements with the combination of several nutrients was also investigated, but there was also no relevance between cases and controls. In the analysis of the association between the consumption of flavonoids, lycopene, vitamin B2 and vitamin C in the benefit of ALS, there were no significant results.

In the same line of study, Okamoto et al. [20] analyzed 153 patients diagnosed with definite or probable ALS, according to the El Escorial criteria base, by applying a food frequency questionnaire to obtain information. As a result, the opposite was observed in the analysis of total fat consumption, referring to saturated, monounsaturated, and polyunsaturated fatty acids, noting that the total percentage of CHO was related to the increased risk of ALS, presenting respectively the value 44.9g for total fat and 13.1g for polyunsaturated fat.

Fitzgerald et al. [21] analyzed 5 large prospective cohort studies, with a total of 995 patients with definitive and probable ALS for 8 years through the application of biennial questionnaires. As a result, the intake of omega-3 PUFA ranging from 1.40 to 1.85 g/day and the intake of omega-6 ranging from 11.82 to 15.73 g/d were observed, where an absence of the relationship between the total consumption of omega 6 and the risk of ALS. Conversely, however, intakes of alpha-linolenic acid (ALA) and omega 3 from marine sources were found to be associated with a lower risk of ALS. Accordingly, if 0.5% of omega 3 is added and a constant intake of omega 6 in the diet is maintained, the risk of ALS is reduced by 34%.

In studies by Nieves et al. [22], 302 patients diagnosed with ALS were analyzed based on El Escorial scores for 5 years using the ALSFRS-R score and the Food Frequency Questionnaire (FFQ). As a result, it was verified that the antioxidant index and the carotene index were positively related to the ALSFRS-R score, also including the micronutrients considered good, such as vitamin A, vitamin E and omega-3 fatty acids, in which a total of 72g of total fat and 1.1-1.6g of polyunsaturated fat were obtained. Likewise, these micronutrients were positively related to the percentage of respiratory function (FVC).

In addition, Nelson et. al. [23] carried out a study with 180 patients diagnosed with ALS through a structured interview and the application of a self-administered food frequency questionnaire. In response to this study, it was addressed that CHO intake was not associated with ALS, however, a relationship was obtained with high protein intake; however, there was no relevance. Regarding the consumption of fats, a positive association of fats with the risk of attenuated ALS was observed and the positive trend towards its risk persisted. The positive correlation with fat intake was largely explained by the contribution of polyunsaturated fats, saturated fats and linoleic acid, in which the study presented 42.2g of total fats and 8g of polyunsaturated fats.

In another study, Huisman et. al. [24] analyzed 674 patients diagnosed with probable or definitive according to the revised criteria of El Escorial, using a food frequency questionnaire (FFQ). In this context, it was exposed that the highest intake of total fat, saturated fat, trans fatty acids and cholesterol, referring to 10.33g of total fat and 1.33g of polyunsaturated fat, were freely associated with an increased risk of ALS, with a higher intake of vegetable protein, polysaccharides, fiber and flavonoids and alcohol associated with a lower risk of ALS.

Discussion

According to studies by Ahmed et al. [17], dietary consumption of polyunsaturated fats added to omega 3 can trigger changes in metabolic factors, affecting eating behavior, disease progression and survival. Their results established an inconclusive effect, considering that the increase in previously ingested fat helped pre-symptomatic ALS in relation to the neurodegenerative process.

It is known that, in humans, increased fat intake reflects a response to changes in energy source, as well as peripheral and central changes in lipid metabolism and neuronal signaling, requiring further studies for greater understanding. of these changes, for a possible therapy with the use of omega 3.

On the other hand, studies by Gopinath et al. [25] demonstrated a correlation between C-reactive protein concentrations and higher intake of omega 3 fatty acids, with a 29% decrease in systemic inflammation being observed. Related to this, alpha-linolenic acid (ALA) has been shown to exert beneficial and significant factors in the production of cytokines; where it showed a decrease in cell adhesion, factors related to the etiology of Amyotrophic Lateral Sclerosis.

Similarly, Pupillo et. al. [18] observed an inversely favorable association between the risk of ALS and fat consumption, demonstrating a favorable role for omega 3 in motor neuron function. Also, in a study in mice with standard diets supplemented with polyunsaturated fatty acid that expressed superoxide dismutase-1 (SOD-1), which is normally altered in inherited cases of ALS, demonstrated that fatty acid supplementation significantly delayed the motor neuron pathology, including the preservation of its secondary function during the terminal stage of the disease, which may provide an improvement in the quality of life of affected individuals [26].

In another study, Veldink et. al. [19] was able to demonstrate a highly relevant inverse correlation between PUFA intake and ALS. These data are extremely important, since it is assumed that the pathological processes observed in the disease, including oxidative stress, apoptosis, mitochondrial dysfunction, inflammation, and glutamate excitotoxicity can transmute. In the present study, it was shown that the intake of PUFA's was related to a 50–60% reduction in the development of the disease, with alpha-linolenic acid (ALA),

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) show a mechanism of action in neuroprotection, promoting the attenuation of glutamate excitotoxicity.

Regarding linoleic acid (ALA), it has been shown to protect neurons from kainate-induced cell death, certainly through ion channels that are also activated by riluzole (the only drug used in the treatment of ALS) [19]. In addition, Kathryn C. Fitzgerald et. al.[21] also demonstrated a reduction in the immunoreactivity of pro-apoptotic proteins by increasing ALA intake. Many epidemiological studies show that omega 3 fatty acids in the blood differ significantly between people with normal cognitive functioning and those with some type of cognitive impairment, which could be a biomarker [27].

In another study carried out to evaluate the neurological benefits of omega 3 fatty acids, it was demonstrated that after supplementation with fish oil, the erythrocyte membrane of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) increased respectively 300% and 42%, including greater protection in the central nervous system. These fatty acids, as structural components of neuronal membranes, directly influence cell function, through effects on membrane properties and also by acting as a precursor assembly for lipid-derived messengers. Thus, these compounds offer an interesting concept in potentially new therapeutic approaches in chronic and acute conditions [28].

Currently, it is known that the excitotoxicity of glutamate is one of the possible causes of Amyotrophic Lateral Sclerosis (ALS), since it plays an indispensable role in neural development, synaptic plasticity, learning and memory, presenting itself as the most numerous in the Central Nervous System (CNS), acting as an excitatory neurotransmitter. Its metabolism is controlled through receptors that are located in pre- and postsynaptic neurons and also in glial cells, controlling the time that this amino acid remains in the synaptic cleft, so that a failure in this mechanism will trigger high brain toxicity leading neurons the death [7].

Research on omega 3 fatty acids has demonstrated its beneficial action on the homeostasis of the glutamatergic system in the hippocampus of rats. These researches confirmed that a diet low in omega 3 fatty acids, referring to the entire development of the CNS until adulthood, was able to delay the normal development of glutamatergic synapses, with a decrease in synaptic proteins, resulting in behavioral changes in the adult life of rats, such as hyperactivity behaviors, anxiety, long-term aversive memory deficits, as well as the reduction of DHA levels in the animals' hippocampus. Omega 3 prevention action was observed in alterations on parameters of the glutamatergic system, in which the compound increased the number of glutamate transporters GLAST and GLT-1, as well as prevention of short-term memory deficit in life rat adult [6].

In the verification of dietary risk factors in the pre-diagnosis of ALS, analyzed in a large case-control study in a Japanese population, carried out by Kazushi Okamoto et al. [20], the amounts of poly-fatty acids in the diet were measured. unsaturated fatty acids, noting that the risk of ALS was significantly reduced with a higher consumption of total fatty acids. In this study, it was observed that a high intake of total fat, saturated fatty acids and PUFA's may have a protective factor against the onset of ALS, leading to statistically relevant effects, with a reduction of up to 60% on the risk of developing ALS in the group with the highest total fat intake versus the lowest. It is not clearly known which mechanisms act in favor of this result; however, it is understood that the total intake of fats and fatty acids has a neuroprotective effect. Furthermore, the study also linked CHO consumption, where investigations have shown a correlation between high CHO intake and low-fat content in protecting against the development of ALS.

In a complementary study by Jeri W. Nieves et al. [22], in which the beneficial effect of polyunsaturated fatty acids on ALS was also supported, it was found that the increase in lutein and omega 3 antioxidants were the most highly weighted in the ALSFRS-R Score (ALS Functional Classification Scale, where the progression and severity of the disease is classified), assuming that, in addition to the fatty acid composition of the cell plasmatic membranes, the responses to oxidative stress, excitotoxicity and inflammation, factors associated with ALS, their ingestion may be associated with body fat, which also seems to protect against ALS.

In short, the central nervous system (CNS) is rich in fatty acids, of which DHA stands out the most, participating in crucial processes within mammalian cells, in addition to being the most abundant component of the neuron membrane, in terms of important structural and functional functions. The condition of the cell membrane influences the exchange of neuronal information, the speed of signal transduction and the interaction with proteins, indicating the importance of this compound to obtain the correct performance. Furthermore, DHA is the main polyunsaturated fatty acid present in the cortical substance, representing 15% of the total PUFA's in the human prefrontal cortex, in addition to other polyunsaturated fatty acids, such as EPA and ALA, which are also present in the CNS. In this way, the control of polyunsaturated fatty acids in the human body, including the brain, is essential for optimal nutrition and brain functionality, reducing neuroexcitotoxicity and neuroinflammation and activating anti-apoptotic pathways [29-30].

Still in relation to the above, but in a negative way, studies by Nelson, et. col. [23] and Huisman, et. col. [24] reported a positive association between fat consumption and the risk of ALS. Individuals with the highest intake of dietary fat had a 3x greater risk of ALS compared to individuals with the lowest intake. The finding of a considerable dose response with fat consumption is curious, because the brain is particularly susceptible to oxidative damage due to relatively high concentrations of polyunsaturated fatty acids, which are particularly prone to lipid peroxidation.

Furthermore, considering that the brain consumes ¼ of the total oxygen intake of the body, but has partially low levels of antioxidant enzymes when compared to other tissues, it is observed that membrane levels of polyunsaturated fatty acids are prevalent in large part by ingestion dietetics. Therefore, dietary consumption of higher concentrations of polyunsaturated fatty acids would be able to increase the amount of brain lipid substrate, which could help to expand lipid peroxidation [23].

This negative result is also confirmed by other studies, which demonstrated the detection of significantly greater vacuolization in the supplemented mice, suggesting an additional increased cell damage within the spinal cord when the animals ingest the fatty acid, so that the predominant effects of EPA on this animal

model of ALS was considered more harmful than neuroprotective[2]. Still in proportion to the study with in vitro animals, it was shown that fatty acids promoted the formation of aggregates of SOD1 mutants in a dose-dependent manner, implying the close involvement of SOD1 aggregates in the pathogenesis of ALS [31].

Conclusion

In view of what has been verified in the literature with studies in humans, the study aims to disseminate under systematic verification, the neuroprotective role of omega 3 against a neurodegenerative pathology, such as Amyotrophic Lateral Sclerosis (ALS). Finally, it is concluded that dietary omega 3 can contribute, that is, by alleviating the symptoms and/or progression of the disease, however, more clinical studies directed directly at this intervention must be carried out, to support the results found.

Conflict of interest

We declare that the article has not been submitted for publication in another journal; and that there is no conflict of interest regarding the publication of this work.

Declaration of role played by each author

We declare that each author (a) contributed significantly to the conception and design of the study and/or to the analysis and interpretation of its results; (b) substantial contribution to the production of the article, or critical review of its intellectual content, and (c) approval of the final version to be published.

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