SESSION 9B EXERCISE, METABOLISM AND NUTRITION

C82 IS EXERCISE A PREDISPOSING FACTOR IN ALS? THE CASE FOR

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Keywords: exercise, physical activity, risk

ALS is a neurodegenerative disorder of the adult life. The cause of ALS in sporadic cases is still unknown. Among the possible causes, physical exercise, including sport activity, has been considered a predisposing factor. From the epidemiological point of view, several case control and cohort studies have evaluated the relationship between ALS and physical activity/sport participation. Most of these studies demonstrated an increased risk for heavy physical activity, with an odds ratio ranging from 1.5 to 2. While these data tend to support some effect of physical activity on ALS risk, these studies have several pitfalls, including the selection of cases and controls, the different operative definition of physical activity and the possible effect of confounding factors. According to one study (1) physical activity may be associated with an earlier age at onset of ALS. Cohort studies on professional athletes (soccer, bicycle riding, American football, basketball) did not demonstrate any specific effect of professional sport activity in ALS, since only professional soccer has been related with ALS (2,3). However, in this study the young age of onset of ALS in soccer players could indicate an effect of anticipation of ALS presentation related to strenuous physical activity. Physical activity could increase motor neuron degeneration because of stimulation of motor neurons in a pre-existent excitotoxic environment. Furthermore, physical activity may lead to increased motor neuron death through an unbalance between free radical formation and radical scavenger systems, with a consequent increased oxidative stress.

Data on the pre-clinical models of ALS are intriguing. In a study comparing $SOD1^{G93A}$ mice under enriched vs. standard conditions better motor performances were observed in the preclinical phase, but an early age at onset of symptoms and a lower survival was observed in female mice (4). This finding has been explained by increased motor neuron firing rates and activity induced by environmental enrichment that may accelerate excitotoxicity. In another study, using the same animal model, male endurance-trained mice had an hastened death compared to sedentary mice (5). Conversely, a study (6) showed that regular exercise significantly increased the life span in $SOD1^{G93A}$ male mice. Therefore, we have no unequivocal indication from the preclinical model of ALS on the effect of exercise on the onset and the course of neurodegeneration.

Data on physical activity and ALS are still too sparse and contradictory to be able to give a firm conclusion. Future epidemiological studies, looking at physical activity with a sound design, as well studies on the possible biological effect of physical activity on motor neurons are warranted.

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C83 IS EXERCISE A PREDISPOSING FACTOR FOR ALS? THE CASE AGAINST

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Keywords: exercise, risk factor

The notion that exercise could be a risk factor for developing ALS may have been supported by the case of Lou Gehrig, the famous American baseball player with ALS who dramatically became manifest during a match when failing to hit the ball. A relationship between exercise and ALS has been suggested by Italian investigators who did a retrospective study of the occurrence of ALS in all Italian professional football players from the series A and B in the period between 1970 and 2001. Risk of developing ALS was higher (1). In a prospective extended study of the original cohort they identified 2 new cases. Mean onset was almost 20 years lower compared with population studies (2). Interestingly, they identified no ALS cases in large control cohorts of professional road cyclists and basketball players. Whether a relationship between exercise and ALS exists, cannot be concluded from these studies. We found no relationship between lifetime physical activity and sporadic ALS (3). However, increased leisure time activities were associated with earlier age at onset. This suggests that premorbid leisure time activities in a population at risk of developing ALS - for other reasons than physical activity – could accelerate onset of ALS.

Experimental studies in hSOD1 mice have not been very helpful to answer this question either (4). Exercise may even be beneficial in terms of survival (4,5). A small clinical trial of resistance exercise showed that patients who trained had higher ALSFRS and SF-36 scores (6). A beneficial effect of training has been demonstrated in other neuromuscular diseases, e.g. Guillain-Barré syndrome, myasthenia gravis and some muscular dystrophies (7). Psychological factors may play a role. Two Cochrane reviews failed to demonstrate a beneficial effect of exercise programmes on functional ability in patients with peripheral neuropathy or muscle disease (8,9). There were no adverse effects. Aerobic training was not well tolerated in patients with Kennedy disease (10).

ALS is considered a multifactorial disease with identified and unidentified risk factors. Identified risk factors include the male sex, smoking, and genetic factors. The next 5 years will reveal what other genetic factors are implicated and what functions these genes have. Excitotoxicity from various causes may induce neuronal death. Mitochondrial dysfunction may be a final common pathway. Disturbance of axonal transport can be a second mechanism. When reinnervation fails, skeletal muscle weakness in ALS results from a shift towards denervation of muscle fibres. The insulin-growth factor I

could act at the level of the muscle fibre or on axonal outgrowth.
Prolonged neuronal excitation in epilepsy can lead to post-ictal paresis, but not to permanent deficit in itself. In conclusion, exercise cannot be held responsible for development of ALS.

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C84 HYPERMETABOLISM IN ALS: IMPLICATIONS FOR NUTRITIONAL MANAGEMENT

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ALS is increasingly recognized as a multi-system disorder. Beyond neurodegeneration, ALS patients display striking alterations of their energy homeostasis, including increased energy expenditure (hypermetabolism) and hyperlipidemia (1–5). Such abnormalities are also found in ALS animal models (6, 7), suggesting that they are intrinsic to the disease process. Most importantly, increasing energy intake of mutant SOD1 mice mitigated their symptoms (7) and increased lipemia positively correlated with survival in a cohort of 385 ALS patients (5). The importance of these findings for defining potential therapeutic strategies and improving nutritional management of ALS patients will be discussed, along with new results showing that muscle hypermetabolism is *per se* sufficient to drive motor neuron degeneration (8).

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C85 PROGNOSTIC SIGNIFICANCE OF NUTRITIONAL PARAMETERS IN ALS PATIENTS

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Keywords: bioimpedance, phase angle, hydration

Background: Malnutrition has been shown to be associated with a poor survival of ALS patients. Malnutrition can be easily evaluated with % of weight loss or body mass index. Other more sophisticated methods have been used to assess the nutritional status of ALS patients. Of those, total body impedance analysis has been validated to assess lean mass and evaluate phase angle, a marker reflecting the nutritional status and the cellular membrane alteration.

Objective: Our aim was to assess the independently prognostic significance of nutritional parameters in survival of patients suffering from ALS.

Methods: Our study included all patients with available nutritional evaluation during their follow up in our referral center located in France. Evaluated variables were body mass index, weight, tricipital skin-fold thickness, midarm muscular circumference, phase angle, lean mass, hydration disorders (extracellular to intracellular water ratio (E/I)). We used the Cox proportional hazard model to perform a survival analysis from time of diagnosis until death or censoring time. We considered variables collected at first evaluation as fixed variables and during the entire follow up as time varying covariates. Our analyses were adjusted on sociodemographic characteristics and neurological clinical status at baseline.

Results: Among 175 patients with at least one nutritional evaluation, we identified that an increase in phase angle was significantly and independently associated with a better survival and that hydration disorders (extracellular to intracellular water ratio (E/I) increment) were significantly associated with a shorter survival.

Discussion: The identification of new prognostic factors of ALS may be useful for clinicians to monitor nutritional status of ALS patients and for researchers to emphasize new hypotheses on the physiopathology of the disease.

C86 DIET AT TIME OF PROCEDURE PREDICTS COMPLICATIONS AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY PLACEMENT IN ALS

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Keywords: percutaneous endoscopic gastrostomy, dysphagia, outcomes

Background: The current ALS practice parameters of the American Academy of Neurology state that PEG is indicated for patients with ALS who have symptomatic dysphagia and should be considered soon after symptom onset. These parameters state that PEG should be placed while the patient's vital capacity is still above 50% of predicted in order to ensure optimal safety and efficacy.

Objectives: The goal of this retrospective study was to assess predictors of outcome and survival after PEG placement at a single center.

Methods: Patients with probable or definite ALS seen between January 2006 and April 2009 were identified by chart review. Forced vital capacity (FVC), ALS Functional Rating Scale score, diet and BMI were captured at time of diagnosis and at time of procedure. The primary outcome measure considered was the presence of any complication (pulmonary, PEG-related, prolonged hospital stay, tracheostomy, and/or death).

Results: Fifty-eight patients (29 female, 29 male) had PEG tube placement. The mean age of patients was 56 ± 13.3 years. Of these, 16 (27.6%) patients had bulbar onset of disease. Indication for PEG tube placement was weight loss in 39 (67%) patients, FVC $<50\%$ of predicted in 11 (19%), and elective placement in 8 (14%). Diet at time of PEG tube placement was regular in 18 (33%) patients, dysphagia level 3 in 24 (44%), dysphagia level 2 in 6 (11%), dysphagia level 1 in 1 (2%), and NPO in 5 (9%). The rate of decline in BMI was 0.2 ± 0.5 units per month (median 0.2, range 1.2 lost to 2.3 gained). The best predictor of complications from PEG placement in our patient sample was the consistency of diet at time of PEG. The more impaired the diet, the higher the likelihood of having at least one complication ($p = 0.02$), and pulmonary complications in particular ($p = 0.005$). The odds ratio for perioperative complications with significant modification in diet (dysphagia level 2, dysphagia level 1 or NPO) was 7.9 (CI: 1.9 to 33.4; $p = 0.005$) and increased after controlling for indication for PEG placement. FVC at time of diagnosis or time of PEG placement or impaired FVC ($<50\%$) was not predictive of perioperative complications or survival ($p > 0.40$). Six month survival was 69% and was correlated with total weight loss between diagnosis of ALS and PEG placement ($p = 0.03$) and rate of weight loss ($p = 0.02$), as well as a slower rate of disease progression ($p = 0.05$) and the absence of any complications ($p = 0.03$).

Conclusions: In our sample, consistency of diet was a more reliable predictor of complications after PEG placement than reduced FVC and may be a good proxy for airway clearance. Careful monitoring of weight and placement of PEG prior to significant adjustment in diet may help prevent perioperative complications and improve 6 month survival.