



## IS PHYSICAL ACTIVITY A RISK FACTOR FOR AMYOTROPHIC LATERAL SCLEROSIS?

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**ABSTRACT**

**Introduction:** Physical activity is controversial with respect to ALS. Our objective was to elucidate the historical profile of habitual physical activity in people with ALS.

**Methods:** A retrospective study was performed involving 97 patients and 105 control individuals. Patients were evaluated with the Baecke questionnaire on habitual physical activity (HPA) in four different periods.

**Results:** Patients with ALS performed more HPA from 10 to 20 years, especially occupational physical activity (OPA), and more OPA from 21 to 30 years than the control group. The type of OPA that was most directly related to the development of disease was rural work (30% of patients) from 10 to 20 years.

**Discussion:** A history of intense habitual physical activity, especially OPA, among patients with ALS suggests a link between these activities and the more early development of disease, as well as increased special care needs among affected patients.

**KEYWORDS :** physical activity; amyotrophic lateral sclerosis; motor neuron disease.

**Introduction**

Motor neuron disease (MND) represents a wide and heterogeneous group of neurodegenerative disorders resulting from functional or structural damage to upper motor neurons, lower motor neurons, or both. Amyotrophic lateral sclerosis (ALS) is the most common [1] and important presentation of motor neuron disease, as well as the most extensively studied motor neuron disease. [2,3]

Despite the existence of common neuropathological bases and presentations for most cases of the disease, new clinical, genetic and pathophysiological data have recently shown that ALS has a multifactorial basis; [4,5] moreover, the roles of individual, environmental and familial risk factors in ALS are poorly understood. [6,7] Although multiple studies regarding the possible neurogenetic mechanisms underlying the development of ALS, [8,9] as well as studies regarding the roles of occupational and physical activity, behavior patterns and diet in the development of the disease, have been undertaken, much controversy still exists regarding ALS and its possible risk factors.

It is known that physical and occupational activities frequently play important roles in the development of different acquired neurological disorders, [10] despite difficulties in assessing the severity of these diseases. [11,12] Traumatic activities, [13,14,15,16,17,18] including sports activities, have been widely studied as triggers or risk factors for the development of dementia or motor syndromes. [19,20,21] However, detailed studies correlating habitual physical and occupational activities as possible risk factors for the development of ALS/MND are still lacking, and more uniform results are needed. [22,23] The aim of this study was to elucidate the historical profile of habitual physical activity in patients with ALS/MND and their variants compared with healthy subjects and to establish a relationship between the durations and intensities of these activities and the time from the presymptomatic period to the development of initial motor symptoms.

**Methods**

A retrospective study approved by our Institutional Ethics Committee in Research involving 202 subjects, including 71 with sporadic ALS (73.2%), 18 with sporadic progressive bulbar palsy (PBP) (18.5%), 8 with familial ALS (8.3%), and 105 healthy individuals without familial MND who served as a control group, was performed. We included patients with definite or probable ALS according to the modified El-Scorial criteria, [24] patients with bulbar-onset or classical spinal-onset PBP, and patients with familial ALS, regardless of the underlying genetic mechanism. All patients selected for this study provided informed consent and were followed with routine neurological evaluations every three to four months between January 2013 and August 2015 in the Motor Neuron Disease Unit, Division of Neuromuscular Diseases, Universidade Federal de São Paulo (UNIFESP). Patients with atypical clinical presentations or with moderate to severe cognitive deficits were excluded. The control group comprised healthy men and women from 40 to 60 years, who were selected using personal invitations or electronic releases to inviting individuals to complete an online questionnaire (available at URL: <http://betofisio.xpg.uol.com.br>). The patients involved in this study could participate virtually via the Internet (Google Docs archive) or via personal contact with an interviewer.

A complete profile analysis involving epidemiological and medical neurological data was performed and verified, and all participants completed the Baecke questionnaire [25] regarding habitual activity pertaining to four different periods of life: (i) from 10 to 20 years, (ii) from 21 to 30 years, (iii) during the last 2 years before first motor symptom onset (2YBSO) and (iv) during the last 12 months before evaluation (12M). Different demographic, general clinical, nutritional [26,27] and neurological assessments were also performed, including assessments of previous ALS/MND hallmarks, for each patient.

The evaluation of habitual physical activity was verified by applying the Baecke questionnaire, [28] which characterizes personal physical

activity history in a retrospective fashion at the following three main levels: occupational physical activity (OPA), items Vq1 to Vq8; physical exercise and leisure activity (PEL), items Vq9 to Vq12; and physical leisure activity and locomotion (LLA), items Vq13 to Vq16. After evaluating each level, a total score of habitual physical activity (HPA) was obtained by adding together the scores for each of the three levels. The formula for the Baecke questionnaire is as follows:

$$OPA = \frac{vq1 + (6-vq2) + vq3 + vq4 + vq5 + vq6 + vq7 + vq8}{8}$$

$$PEL = \frac{vq9 + vq10 + vq11 + vq12}{4}$$

$$LLA = \frac{(6-vq13) + vq14 + vq15 + vq16}{4}$$

$$TS = OPA + PEL + LLA$$

We also evaluated the final scores for each of the four assessed periods of life. Habitual physical activity intensity was classified according to previous studies; [28] cases that were not covered in Baecke's classification were evaluated by two other studies. Ainsworth's evaluation provided complete data regarding energy expenditure during many physical activities. [29,30,31] McArdle's evaluation classified energy expenditure based on multiple metabolic rates at rest (mets) to determine the minimum requirements to keep an individual stable at rest. [32]

Two statistical analysis programs (SPSS 11.0 and GRAPH PAD PRISM version 5.03) were used, and different statistical analyses were performed, depending on the different correlations and variables under study (Kolmogorov-Smirnov, Pearson's chi-squared, Mann-Whitney, Kruskal-Wallis, Anova, Friedman, Spearman's correlation, Kendall's correlation, Cronbach's alpha coefficient, and correlation coefficient).

## Results

A summary of the social and demographic data is presented in table 1.

### TABLE 1

A significantly higher proportion of patients with ALS presented with type of work or occupation (vigorous) between 10 and 20 years compared with the control group ( $p < 0.001$ ), although the same relationship was not observed between 21 and 30 years. However, when comparing OPA scores over time, there were significant differences from 10 to 20 years and 21 to 30 years and during the last 12 months ( $p < 0.001$ ) between the groups. (Figure 1)

### FIGURE 1

There was a significant difference in the performance of type of work or occupational (moderate) between the healthy controls and the MND patients during the last 12 months before evaluation ( $p = 0.005$ ), showing a decrease of physical capacity of patients due to the onset of the disease. In the ALS/MND group, 27.8% of patients performed rural work, and 10% were students between 10 and 20 years, while the control group was dominated by intellectual professions, as students (23.8%), office clerks (10.5%) and banking professionals (6.6%) during the same period. In the ALS/MND group, 9.2% of patients were house workers, and 5.1% were teachers, masons, maids (housekeeper) and administrators between 21 and 30 years, while the control group was dominated by teachers (9.5%), secretaries (6.6%) and banking professionals (5.7%) during the same period (intellectual professions). During the last two years before symptom onset, the ALS/MND group was dominated by retired individuals (14.4%), houseworkers (9.2%), drivers (8.2%) and merchants (7.2%), whereas during the last twelve months, the main occupational physical activity was retirement (69.1%) in the same group. In the healthy control group, the most common occupational physical activities were teaching (8.6%), retirement (5.7%) and trade management (3.8%) during the same period. Rural work between the ages of 10 and 20 years was the most common activity noted among sporadic and familial ALS and PBP patients, while between 21 and 30 years, housework was the most common activity noted among patients in the ALS group (9.8%). Maids predominated in the PBP group (16.6%), and masons predominated in the familial ALS group (25.0%).

Figure 2 shows the average distributions of HPA scores throughout life. It appears that the mean scores behaved similarly in the ALS/MND group, but there are significant differences from the control group from 10 to 20 years and during the last 12 months.

### FIGURE 2

The HPA score in patients from 21 to 30 years showed a "very high" negative association with initial symptom onset, indicating that patients with familial ALS who were more physically active experienced earlier symptom onset. For the PBP group, a "moderate" negative association was found between the OPA (2YBSO) score and "first motor symptom onset", indicating that patients with PBP who performed more occupational physical activity during the last two years before symptom onset experienced earlier symptom onset. (Table 2)

### TABLE 2

An assessment called "key events" was created, an event that denotes worsening of the disease, as use of a wheelchair, hospitalization, mechanical ventilation, tracheostomy submission among others. It calculated the period from the beginning of the first symptoms until the date of the event, thus denoting the worsening of the disease, obtained data from the clinical history of the patient. Correlations relating to key events indicate that those who performed more LLA (10 to 20) ("moderate" correlation), mainly men ("high" correlation), later used a wheelchair. Patients who engaged in more HPA (12 m), especially OPA (12 m), required a wheelchair earlier, showing a moderate correlation between these parameters. Patients who engaged in more HPA (12 m) used noninvasive mechanical ventilation (NIMV) earlier, showing a strong correlation between these parameters. Patients who engaged in more HPA (12 m) underwent percutaneous endoscopic gastrostomy (PEG) earlier, showing a high correlation between these parameters. (Table 3)

### TABLE 3

## Discussion

The epidemiological data from our sample of ALS patients were in accordance with those of previous studies in Brazil and worldwide regarding gender, ethnicity and age at disease onset. [33,34,35,36] There was also homogeneity regarding epidemiological, nutritional and clinical data among all MND patients. Most cases were represented by defined ALS cases applying the modified El-Escorial criteria, showing that the data from this sample are reliable and representative of familial and sporadic ALS and PBP cases.

Subgroup analysis indicated that the ALS/MND group presented with more vigorous occupational physical activity from 10 to 20 years and 21 to 30 years than the healthy controls. It is noteworthy that nearly 28% of cases presented with vigorous intense activity (10-20 years), with a marked prevalence of rural work, regardless of subtype (ALS = 22.5%; PBP: 33.3%; FAMILY: 25%). Occupational physical activity was also found to be higher from 21 to 30 years in patients with ALS/MND than in control subjects, indicating that vigorous professional physical effort was not limited only to rural work. Other vigorous occupations, such as housekeeper, locksmith, metalworker, machine operator, general assistant, and mason, predominated during this period. However, as other exposures and risk factors are associated with these occupations, such as neurotoxicity, it is not possible to attribute the development of ALS to only occupational physical activity. [21]

There was a marked progressive decline in all habitual physical activities during the last 12 months for all groups, particularly for the sporadic ALS group, in which all patients presented with moderate activity. Thus, disclosing a well-known early complication clinical of sporadic ALS in relation to familial ALS and PBP.

Regarding the last 12 months before symptom onset, the healthy controls presented with higher scores for each physical activity than the ALS patients. The PBP group presented with better clinical conditions and physical activity scores during the last 12 months than the sporadic ALS group, and the same was true when comparing on the local of the first symptom, patients with bulbar onset and column showed better habitual physical conditions than those starting in the lower limbs, appendicular beginning. Other results showed that PBP patients who engaged in more intense physical activities during the last two years before symptom onset presented with earlier motor symptoms. Similarly, familial ALS patients who engaged in more intense habitual physical activity between 21 and 30 years or more intense leisure activities between 21 and 30 years presented with earlier motor symptoms than healthy control subjects, findings in

accordance with those of previous studies. [37] It has been shown that more intense habitual physical activity results from better physical aptitude, which increases susceptibility to developing sporadic and familial ALS.

It has also been shown that patients who engaged in more intense habitual physical activity during the last 12 months presented with earlier percutaneous endoscopic gastrostomy, earlier wheelchair use and earlier non-invasive ventilation, thus demonstrating marked disease progression in the context of recent intense physical activities.

It is reasonable to consider that more intense physical activities may precipitate marked motor denervation and severe functional compromise.

**Conclusions**

Although the roles of habitual and occupational physical activities in the development of ALS and its clinical variants remain controversial, we showed that there is a strong association between disease development and severity and a history of more intense physical activity, especially occupational activity.

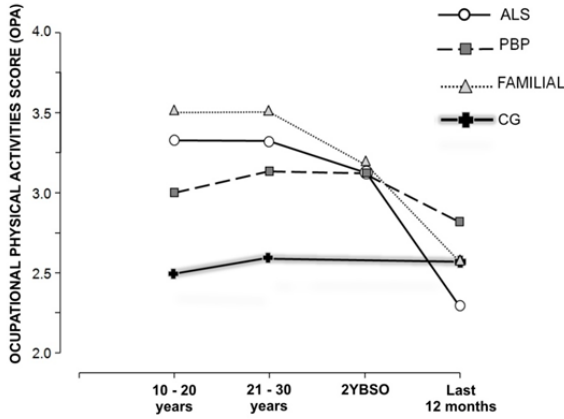


Figure 1 - Median Distribution of OPA scores of groups for period.

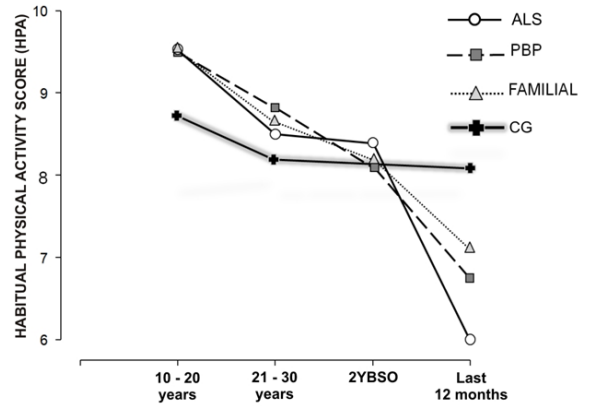


Figure 2 - Median Distribution of HPA scores of groups for period.

Table 1: Sociodemographic characteristics of survey participants.

CHARACTERISTICS	ALS/MND (N=97)		CG (N=105)		Total (N=202)		Value p
	N	%	N	%	N	%	
<b>Gender</b>							
Male	55	56,7	55	52,4	110	54,6	> 0,05
Female	42	43,3	50	47,6	92	45,4	
<b>Ethnic</b>							
White	79	81,4	94	89,5	173	85,7	(a) * < 0,04
Brown	10	10,3	10	9,6	20	9,9	
Black	8	8,3	1	0,9	9	4,4	
<b>Age range (years)</b>							
28 - 45	12	12,4	27	25,7	39	19,3	(b) * < 0,001
46 - 56	39	40,2	58	55,2	97	48,1	
57 - 78	46	47,4	20	19,1	66	32,6	
<b>Education (years of formal schooling)</b>							
0 - 8	48	49,5	3	2,8	51	25,2	(c) * < 0,001
9 - 12	27	27,8	12	11,4	39	19,3	
13-a 16	20	20,6	11	10,5	31	15,4	
17 and more	2	2,1	79	75,3	81	40,1	
<b>Type of work or occupation (10 to 20 years)</b>							(d) * < 0,001
Easy	38	39,2	83	79,1	121	59,9	
Moderate	32	32,9	21	20,0	53	26,2	
Severe	27	27,8	1	0,9	28	13,8	
<b>Type of work or occupation (21 to 30 years)</b>							> 0,05
Easy	47	48,4	62	59,1	109	53,9	
Moderate	44	45,4	36	34,3	80	39,7	
Severe	6	6,2	7	6,6	13	6,4	
<b>Type of work or occupation (last 2 years before the first motor symptom onset - 2YBSO)</b>							
Easy	58	59,8	-	-	-	-	
Moderate	32	32,9	-	-	-	-	
Severe	7	7,2	-	-	-	-	
<b>Type of work or occupation (last 12 months before evaluation)</b>							(e) * 0,005
Easy	84	86,6	73	69,6	157	77,8	
Moderate	12	12,4	29	27,6	41	20,3	
Severe	1	1,0	3	2,8	4	1,9	

Pearson's chi-square test. \* = significant p value. (a) White vs Black; (b) 57 - 78 vs 28 - 45/46 - 56; (c) 0 - 8 vs 9 - 12/13 - 16/17 and more; (c) 9 - 12 vs 17 and more; (c) 13 - 16 vs 17 and more; (d) Easy vs Moderate/Severe; (d) Moderate vs Severe; (e) Easy vs Moderate.

**Table 2:** Spearman correlation coefficients and p values between scores of the Baecke and the variable "first motor symptom onset".

CORRELATIONS BETWEEN VARIABLES		
GROUPS / SCORES	FIRST MOTOR SYMPTOM ONSET	
	r	Value p
PBP / OPA (2YBSO)	-0,497	<b>0,035</b>
FAMILIAL / HPA (21 - 30 years)	-0,764	<b>0,045</b>

Note: PBP: progressive bulbar palsy; OPA: occupational physical activity; 2YBSO: last 2 years before the first motor symptom onset; HPA: habitual physical activity.

**Table 3:** Spearman correlation coefficients and p values between scores of the Baecke and the variable "key events".

EVENTS	CORRELATIONS OF KEY EVENTS							
	Male		LLA(10-20)		OPA(12m)		HPA(12m)	
	r	p	r	p	r	p	r	p
Wheelchair	0,535	<b>0,002</b>	0,414	<b>0,025</b>	-0,458	<b>0,012</b>	-0,484	<b>0,007</b>
NIMV							-0,610	<b>0,007</b>
PEG							-0,697	<b>0,043</b>

Note: LLA: physical leisure activities and locomotion; OPA: occupational physical activity; HPA: habitual physical activity; NIMV: noninvasive mechanical ventilation; PEG: percutaneous endoscopic gastrostomy.

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