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Amyotrophic lateral sclerosis, physical exercise, trauma and sports: Results of a population-based pilot case-control study

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Abstract

Our objective was to investigate exposure to physical exercise and trauma in patients with amyotrophic lateral sclerosis (ALS) compared to the general population. Previous studies in this area have yielded conflicting results. Using population-based ALS registries from Italy, the UK and Ireland, newly diagnosed patients with definite, probable or possible ALS were enrolled in a case-control study with two age- and sex-matched controls for each patient. Source, intensity and duration of physical activity and history of trauma were recorded. We here present the results of a pilot investigation. We studied 61 patients and 112 controls. Forty-one per cent of cases and 17.0% of controls ($p = 0.001$) had blue-collar occupations; 13.1% versus 3.6% reported strenuous physical activity at work ($p = 0.05$). Compared with controls, ALS patients had a longer exposure to work-related (10.7 vs. 7.3 years; $p = 0.02$) and sport-related physical exercise (9.6 vs. 5.2 years; $p = 0.005$). Three patients (0 controls) reported professional sports ($p < 0.04$). Traumatic events were similar. Blue collar occupation (OR 4.27; 95% CI 1.68–10.88) and duration of sport-related physical exercise (OR 1.03; 95% CI 1.00–1.05) were independent variables in multivariate analysis. We concluded that ALS is associated with physical exercise but not with traumatic events.

Introduction

Since the observation of eight deaths due to amyotrophic lateral sclerosis (ALS) among 24,000 professional soccer players in Italy (1), a number of studies have been performed to further investigate the correlation between ALS, physical exercise, and trauma. Some of these have confirmed that the risk of ALS is higher than expected in professional soccer players and university athletes (2–4). Others have failed to confirm these findings (5,6). These conflicting reports may be explained by a number of factors, including selection bias, low exposure rates, incorrect selection of cases and controls, and lack of standardization in the definition of exposure (7).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

A large population-based case-control study is being performed to obtain definitive answers to these questions using a targeted, semi-structured form and interview. To finalize the study design, a pilot study was undertaken with the following aims: 1) to check the feasibility of the procedure adopted to identify cases and controls; 2) to verify the quality and completeness of data recording; 3) to define the extent of exposure to the putative risk factors expected in the general populations; and 4) to calculate the sample size required for each given exposure to prove a significant association between ALS, physical exercise, and trauma. The results of this pilot investigation are presented here.

Material and methods

The patients were recruited from people with newly diagnosed ALS± attending centres participating in the EURALS Consortium. This is an international collaboration between national and regional population-based registries located in Italy, England, Scotland, and Ireland (8). Given the fairly large size of the population at risk (in excess of 25 million), EURALS can identify up to 500 newly diagnosed ALS patients annually. To be enrolled in the pilot study, patients had to satisfy the criteria for definite probable, or possible ALS according to the El-Escorial criteria (9).

Two age (+/- 2.5 years) and sex-matched controls were identified for each ALS patient. These were selected in conjunction with the ALS patients' general practitioners (GPs) to ensure they were a representative sample of the general population. All participants gave informed consent.

The cases were a sequential sample of patients with newly diagnosed ALS eligible for registration. Controls were selected by approaching the GPs by telephone in the regions where the patients lived and asking them to identify on their lists individuals matching the patients to be contacted. Where this was not possible, the research coordinator visited some GP surgeries and investigated the lists with the secretary, seeking to identify matched controls from the same geographic regions. In rare instances in Italy, when GPs' lists were unavailable, controls not traceable through the GPs' lists were selected from other sources (e.g. relatives or friends). There were virtually no cases and less than 10% of controls refusing participation in the study.

An arbitrary decision was made to stop recruitment when about 60 cases and 120 controls had been enrolled in the study. This sample size was sufficient to check the feasibility of the study and give it enough power to detect a 15% difference in the exposure to strenuous physical activity between cases and controls.

A standardized semi-structured form was devised to generate a full history of the exposures. The questionnaire included relevant demographic data (age, sex, residency, education, occupation, physical activity and sport profile) and clinical data (age at onset of symptoms, site of onset, El-Escorial diagnostic category – definite or probable ALS). A detailed history of each employment was collected, including job description, date of commencement and cessation, type, degree of physical activity required (coded as mild, moderate, or strenuous) and hours per month spent in occupational physical activity. A detailed history of each sport was also collected, including type, date of commencement and cessation, degree of physical activity required by each sport (coded as mild, moderate, or strenuous), and hours per month spent in sport physical activity. Cases and controls performing a type of work requiring manual labor and work clothes were then classified as 'blue collar' and separated from the remainder ('white collar').

Physical activity was defined as spending (or having spent) some time engaged in a task causing exertional dyspnoea at least once a month. The intensity of physical activity was

coded arbitrarily, depending on type of occupational and/or leisure activity and the amount of energy spent by the body. Sports were classified as amateur, organized or professional. Records were also taken on drug exposure (limited to compounds taken for at least six months). Cases and controls were contacted either directly or by telephone interview.

Cases and controls were compared for all demographic and clinical variables. Based on proportions, odds ratios (ORs) with 95% confidence intervals (CI) were calculated. In addition, a multivariable logistic regression analysis was performed using the case-control status as the response variable; strenuous work and sport activities, duration of exposure to work-related and sport-related physical exercise, blue collar work, professional sport, repeated trauma, having been a farmer as independent variables; and age, sex and country as covariates.

Results

The study population included 61 cases (34 male and 27 female, age range 33–86 years (mean 63.7 years)) and 112 controls (66 male and 46 female, age range 30–84 years (mean 62.3 years)). The demographic characteristics of the sample are depicted in Table I. The highest proportion of cases and controls was from Italy (36 cases and 67 controls), followed by the UK (17 cases, 30 controls) and Ireland (eight cases, 15 controls). High school or greater education was recorded for 68.9% of cases and 58.4% of controls. In contrast, 41.0% of cases and only 17.0% of controls reported blue collar as the main occupation ($p < 0.001$). Thirty-one cases (48.4%) and 30 controls (27.5%) reported at least one blue collar job during their entire career ($p = 0.005$). The only occupation found to prevail in ALS patients was farming/gardening (eight cases versus three controls; $p = 0.02$). There were no differences between cases and controls with regard to age, marital status, alcohol and tobacco use.

Mean BMI values were fairly similar in the two groups (cases: 25.3, SD 4.5; controls: 26.1, SD 4.1). The types of physical exercise were similar in ALS patients and controls (Table II). In contrast, 13.1% of cases and only 3.6% of controls reported strenuous physical exercise at work ($p < 0.05$). Compared to controls, patients with ALS reported a longer duration of exposure to work-related physical exercise (10.7 years (SD 17.3) vs. 7.3 years (SD 15.2); $p < 0.02$) and sport-related physical exercise (9.6 years (SD 14.4) vs. 5.2 (SD 12.5); $p < 0.005$). No differences between groups were found for intensity of sport-related physical exercise and number of individuals involved in organized sports (see Table II). Three ALS patients (0 controls) reported that they had been professional athletes (soccer, 2; athletics, 1) ($p = 0.04$). The number of patients reporting traumatic events was similar in the two groups (cases, 47.5%; controls, 52.7%) and no differences were found for site of trauma, severity of trauma (including residual disability and hospital admission) and repeated trauma (Table II).

The only variables in the multivariable analysis found to be of significance for ALS patients were blue collar occupation (4.27; 95% CI 1.68–10.88) and duration of exposure to physical exercise during sport (1.03; 95% CI 1.00–1.05).

Discussion

This population-based pilot case-control study suggests that ALS may be associated with a history of physical exertion, but not with repeated traumatic events. Blue collar occupation and duration of physical exercise in sports were independent contributions to this association. Our findings are consistent with others (2–4,10). The mechanism remains unclear. It may be that prolonged exercise is deleterious in some individuals when combined with other environmental factors, such as exposure to pesticides or drugs (11). Nevertheless,

moderate exercise after disease onset can also improve ALS functional disability scores and ameliorate disease symptoms (12–14). However, rats exposed to exhaustive running show an overall reduction in fast axonal transport capability (15). On this basis, one may question that short-lasting physical exercise tends to delay disease progression in diseased animals and humans but prolonged physical exercise may hasten the metabolic requirements of motor neurons and glia. However, motor neurons tend to adapt to exercise at the metabolic level. Motor neurons of treadmill running trained rats display morphological changes consistent with increased protein synthesis (16). The mitochondrial electron-transport chain enzyme succinate dehydrogenase is also significantly increased in exercised skeletal muscle to compensate for the increased energy demands (16). These demands may not be satisfied when stopping physical exercise, thus putting an otherwise susceptible patient at risk of developing the disease.

The major strength of this study is the representativeness of the study population (patients with newly diagnosed definite or probable ALS from population-based registries, and age- and sex-matched controls from the GPs' lists). The selection of newly diagnosed (incident) patients also minimizes differential recall bias between cases and controls. The detailed collection of data relating to all previous physical activity further strengthens the study design. However, as is the case for all studies based on patient recall, this study is limited by the degree of accuracy of information, particularly in those with a degree of cognitive impairment. In addition, many non-significant associations found here may be simply reflected by the low power of the study. Other limitations are the small sample size and the absence of data relating to other exposures, which may contribute to risk.

Nevertheless, these findings provide preliminary data in support of a presumed correlation between physical exercise and risk of ALS, to be confirmed in a larger prospective population-based case-controlled study. Given the quality and completeness of the present data, the protocol of the study does not require major changes. Although proper matching was sometimes difficult, we will still rely on the GPs' lists as the preferred source of normal individuals. In addition, despite the use of arbitrary terms to define some exposure variables (such as mild, moderate and strenuous physical activity), in the absence of better alternatives we will retain these definitions and supplement them with more precise measures of the energy consumed, such as the metabolic equivalents, i.e. the ratios between metabolic rates caused by a given activity and the standardized metabolic rate at rest (1 kcal/kg/h) (17). Finally, based on these results and the size of the population at risk, we expect to recruit 660 cases and 1320 controls over a two-year period under the assumption of an OR of 2 or higher for former professional sportsmen (1% of controls).

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Table I

Demographic characteristic of the sample.

	Cases		Controls	
Variable	n	%	n	%
Total	61	100	112	100
Gender				
Female	27	44.3	46	41.1
Male	34	55.7	66	58.9
Age (years)				
<55	8	13.1	24	21.6
55–74	45	73.8	77	69.4
>74	8	13.1	10	9
Marital status				
Married	45	75	90	81.1
Widowed	7	11.7	6	5.4
Single	5	8.3	11	9.9
Divorced	2	3.3	4	3.6
Living with partner	1	1.7	–	–
NS	1	–	1	–
Education				
None	1	1.6	–	–
Elementary	14	23	31	27.9
Middle	13	21.3	19	17.1
High school	25	41	42	37.8
University	8	13.1	19	17.1
NS	–	–	1	–
Main occupation *				
Blue collar	25	41	19	17
White collar	36	59.2	93	83
Alcohol				
No	43	70.5	88	78.6
Yes	18	29.5	24	21.4
Tobacco				
No	32	52.5	64	57.1
Yes	29	47.5	48	42.9

* $p = 0.001$ (2-sided).

Table II

Physical activity and history of trauma.

	Cases		Controls	
Variable	n	%	n	%
Physical exercise				
No	16	26.2	38	33.9
Work	13	21.2	17	15.2
Sport	23	37.7	46	41.1
Combined	9	14.8	11	9.8
Intensity of exercise (work) *				
None	29	47.5	64	57.1
Mild	12	19.7	30	26.8
Moderate	12	19.7	14	12.5
Strenuous	8	13.1	4	3.6
Intensity of exercise (sport)				
None	24	39.3	47	42
Mild	10	16.4	16	14.3
Moderate	19	31.1	30	26.8
Strenuous	8	35.3	19	17
Organized sports				
No	38	62.3	70	62.5
Yes	23	37.7	42	37.5
Professional sports **				
No	58	95.1	112	100
Yes	3	4.9	–	–
Trauma				
No	32	52.5	53	47.3
Yes	29	47.5	59	52.7
Site of trauma				
None	33	54.1	52	46.4
Head	4	6.6	11	9.8
Chest	1	1.6	3	2.7
Abdomen	1	1.6	2	1.8
Arms	11	18	20	17.9
Legs	11	18	24	21.4
Disability				
No	38	62.3	72	64.3
Temporary	22	36.1	37	33
Permanent	1	1.6	3	2.7

	Cases		Controls	
Variable	n	%	n	%
Hospitalization				
No	44	72.1	74	66.1
Yes	17	27.9	38	33.9
Repeated trauma				
No	40	65.6	85	75.9
Yes	21	34.4	27	24.1

*
 $p = 0.05$.

**
 $p = 0.04$.