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Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players

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Summary

The cause of amyotrophic lateral sclerosis (ALS) is still unknown. A possible relationship between ALS and sport participation has been supposed, but never definitely demonstrated. We studied a cohort of 7325 male professional football players engaged by a football team from the Italian First or Second Division in the period 1970–2001. ALS cases were identified using different concurrent sources. Standardized morbidity ratios (SMRs) were calculated. During the 137 078 person-years of follow-up, five ALS cases were identified (mean age of onset, 43.4 years). Three cases had a bulbar onset, significantly more than expected ($P = 0.003$). Since the number of expected cases was 0.77, the overall SMR was 6.5 [95% confidence interval (CI), 2.1–15.1]. 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, whereas no ALS case was found in the 1970–1979 period. A dose–response relationship between the duration of professional football activity and the risk of ALS was found (>5 years, 15.2, 95% CI, 3.1–44.4; ≤5 years, 3.5, 95% CI, 0.4–12.7). Our findings seem to indicate that playing professional football is a strong risk factor for ALS.

Keywords: amyotrophic lateral sclerosis; risk factor; football

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; SMR: standardized morbidity ratio

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Introduction

Amyotrophic lateral sclerosis (ALS) is an adult onset degenerative disorder of the nervous system with a fatal progressive course. Its cause is still unknown. Hypotheses concerning ALS pathogenesis have been proposed including excitotoxicity, oxidative stress, impairment of neurofilament function, and inflammation (Rowland and Schneider, 2001). Several case control studies have analysed risk factors for ALS, but with inconsistent results (Armon, 2003). Besides aging and male gender, which are well established risk factors, other proposed factors include: mechanical and electrical traumas; professional and environmental exposure to metals, herbicides or other toxic substances; smoking; heavy physical activity; and some professions such as welding, farming and animal breeding (Mitchell, 2000; Armon, 2003). Although sport participation has been supposed a risk factor for ALS since at least the 1970s (Kurtzke and Beebe, 1980), the case control studies assessing the relationship between ALS and sport have failed to provide clear-cut results (Armon, 2003).

Following a complaint by a football coach regarding the diffusion of illegal drugs among football players, an Italian prosecutor, Mr Raffaele Guariniello, who was particularly interested in environmental and health lawsuits, ordered an inquiry in 2000 into the causes of death in a cohort of some 24 000 players who played between 1960 and 1996 in Italian professional and semi-professional football divisions (Series A, B and C). Out of 375 deaths, eight were due to ALS. Using

Italian mortality statistics as a reference, the expected number of deaths was 0.69 and the corresponding standardized proportional mortality ratio was 11.6 [95% confidence interval (CI), 6.7–20.0] (unpublished data). Although this preliminary study had some biases (mainly related to the structure of the football cohort), its results prompted us to perform a retrospective incidence study on ALS in a rigorously defined cohort of Italian professional football players.

Methods

Study subjects

The study cohort included all male professional football players who: (i) were engaged by a football team in the Italian First (Series A) or Second (Series B) Divisions in the period between September 1, 1970 (the start of the 1970–1971 playing season) and June 30, 2002 (the end of the 2001–2002 playing season); and (ii) had played at least one official match. Two concurrent sources were used to determine the study cohort; (i) the archives of the football players pension plan (ENPALS), to which all professional football players have been obligatorily enlisted since June 1983; and (ii) the archives of the Panini Company, the major Italian football cards publisher, which has been in operation since 1961. Football players not born in Italy were excluded from the study, since it was not possible to follow up all of them accurately. In fact, almost all were foreign players, who went back to their home countries after ceasing activity with Italian teams.

For each player, we recorded the date of birth, the age and calendar year at the time of engagement by the professional football team, the playing position (goalkeeper, back, midfielder, forward) and the number of years of activity as a professional football player.

A football player was considered at risk from the date of engagement by a professional football team to either December 31, 2001, his date of death, or the date of onset of ALS. There were no subjects lost to follow-up.

ALS cases ascertainment

Several sources were used to identify ALS cases: (i) death certificates obtained from the Italian Statistics Bureau (ISTAT) for the period 1970–2000 [1970–1978, International Classification of Diseases (ICD)-8 code 348.0; 1980–2001, ICD-9 code 335.2]; (ii) the archives of major Italian ALS centres (Milano, Torino, Veruno); (iii) the archives of the Italian ALS Association; (iv) information provided by media and websites; and (v) self-reports by ALS patients or their relatives.

For each alleged ALS case, complete clinical data were collected, including hospital records. If alive, the patient was interviewed. If the patient was dead, his family members or caring physicians, or both, were interviewed. Detailed information was asked about: the patient's personal and medical history; football activity including playing position and all the football teams he played for (including as an amateur); his work after stopping professional football; and his major physical traumas and drug or environmental toxic exposure related to both work and leisure activities. A detailed family history was also collected, with particular regard to neuromuscular disorders.

To reduce the risk of misdiagnoses, only cases with definite or probable ALS (Brooks *et al*., 2000) were included in the study.

Statistical analysis

Standardized morbidity ratios (SMRs) for the whole population and for each sub-group (time-periods, playing positions, number of years as professional football players) were calculated using as reference the incidence rates of the Piemonte and Valle d'Aosta Register for ALS (northern Italy) (PARALS, 2001), and the Puglia ALS register (southern Italy) (Logroscino *et al*., 1999). These two prospective incidence registers cover ∼8.5 million inhabitants, i.e. 15% of the Italian population. An average of the two registers' incidence rates was used. For calculation of SMRs, five-year age- and gender-specific incidence rates were used (15–19, 20–24, . . . 65–69). Ninety-five percent confidence intervals were calculated assuming a Poisson distribution (Schoenberg, 1983). A two-tailed χ^2 test was used to compare the expected and observed site of onset of symptoms.

Results

Study cohort

The initial cohort included 8366 professional football players who played in the period between 1970 and 2001. After excluding those players who were not born in Italy, the study cohort consisted of 7325 professional football players, whose age, at the last day of the follow-up, ranged from 18 to 69 years.

ALS cases

A total of 18 professional football players who developed ALS during the study period were identified. Three players were excluded since they were not born in Italy (one of them, however, played during the study period). Ten players were excluded because they played before 1970 (Fig. 1).

During the 137 078 person-years of follow-up, five cases were identified. No case was diagnosed in the period 1970–1979, two were diagnosed in the period 1980–1989, and three in the period 1990–2001. The calendar years of onset of ALS for the five cases were 1981, 1984, 1999, 2000 and 2001, respectively. The mean age of onset was 43.4 years (SD 9.1; range 33–56). Three cases had a bulbar onset, two a spinal onset (one each in lower and upper limbs), with a significant excess of bulbar onset compared with the expected distribution calculated using the age-specific data of the two Italian ALS registers (0.7 bulbar and 4.3 spinal onset cases) ($P = 0.003$). None had a positive family history for ALS or other neuromuscular disorders. Interestingly, none had major traumas requiring admission to hospital or had had professional or accidental contact with substances such as metals or solvents, which are generally suspected to be related to ALS. One of the five subjects was still playing professional football when ALS symptoms first occurred. For the other four cases, the time-period between the end of professional football activity and the onset of ALS ranged between 4 and 19 years. On December 31, 2003, four cases were deceased and one was alive. The mean duration of ALS was 32.8 months (SD 8.1) in the four deceased cases; the

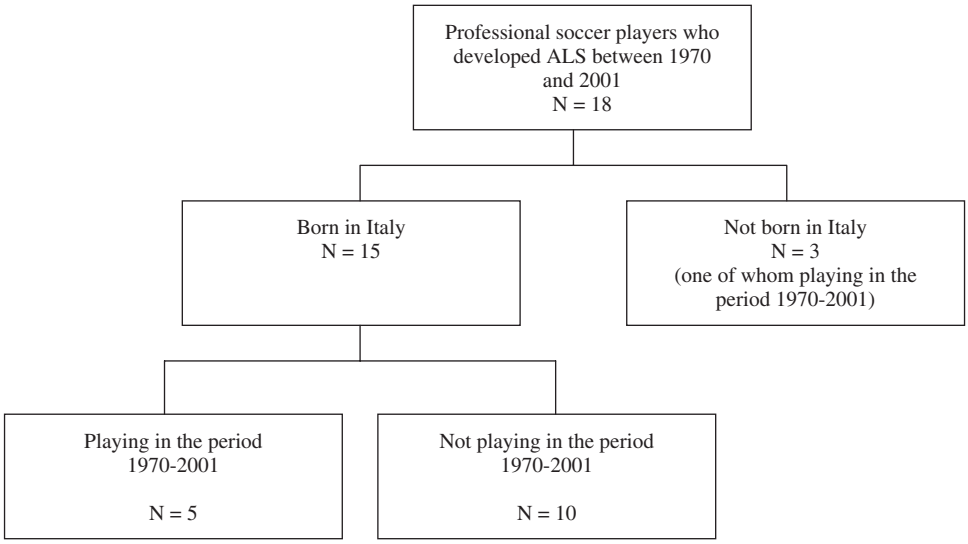

Fig. 1 Study recruitment flow chart. All cases are definite or probable ALS according to El Escorial revised criteria (Brooks *et al*., 2000).

duration of ALS in the only living case was 42 months. No case underwent tracheostomy.

SMRs calculation

Using the incidence rates of the two Italian ALS registers as a reference, the number of expected cases during the period 1970–2001 was 0.77. Therefore, the overall SMR was 6.5 (95% CI, 2.1–15.1).

The SMRs according to age-classes are reported in Table 1. There was a significant increase of SMR for ALS onset before 49 years, whereas the risk for older subjects was not increased. The SMR was significantly increased in the period 1980–1989 and, to a lesser extent, in 1990–2001, whereas no ALS case was found in the first decade of the study (Table 2). When considering the playing position, a significant increase of risk was found only for midfielders (Table 3). A significant relationship between the risk of ALS and a longer duration of professional football activity was found (Table 4).

Table 1 *SMRs by age classes*

Age classes	Expected cases	Observed cases	SMR	95% CI
15–49	0.53	4	7.5	2.0–19.2
50–69	0.24	1	4.2	0.1–23.4

Table 2 *SMRs by period of observation*

Years	Expected cases	Observed cases	SMR	95% CI
1970–1979	0.04	0	–	–
1980–1989	0.14	2	13.8	1.7–49.8
1990–2001	0.59	3	5.1	1.1–14.9

Table 3 *SMR by playing position*

Playing position	Expected cases	Observed cases	SMR	95% CI
Forward	0.09	–	–	–
Midfield	0.33	4	12.2	3.3–31.2
Back	0.24	1	4.1	0.1–23.1
Goalkeeper	0.11	–	–	–

Table 4 *SMR by number of years as a professional football player*

Number of years	Expected cases	Observed cases	SMR	95% CI
⩽5 years	0.57	2	3.5	0.4–12.7
>5 years	0.20	3	15.2	3.1–44.4

Discussion

To our knowledge, this is the first study demonstrating a highly significant relationship between a risk factor (playing professional football) and ALS in a large retrospective cohort. The study was prompted by the casual observation of an increase of risk of dying from ALS in a series of Italian football players. It aimed to analyse the incidence of ALS and its characteristics in a better defined cohort of Italian football players.

The study population included all Italian male football players who were engaged by professional teams and played at least one official match. Foreign-born players were excluded (most of whom were engaged after the late 1980s), since a complete follow-up of these subjects was not possible. However, the inclusion of foreign football players would further increase the SMR, since at least one foreign-born player who developed ALS after having played in the study period was identified.

We considered at risk each football player from the date he was engaged by a professional team up to the last day of the follow-up, even if he had played only a single official match (thus reproducing an intention-to-treat procedure).

The case finding in this study is a mix of the classical methodology based on active ascertainment (i.e. search from death certificates, ALS centre archives and ALS association register) and the so-called spider methodology, based on passive ascertainment (i.e. cases found through self-reporting to the investigators). The latter methodology was possible due to the large publicity given by mass media in Italy to the findings of the unpublished preliminary study based on death certificates. However, the possibility of an underestimation of cases in the first decade of the study cannot be ruled out; this could partly explain the absence of ALS cases in the period 1970–1979.

The SMR found in our study is the highest so far observed for any alleged risk factor for ALS. A clear dose–response relationship between the length of the period of activity as a professional and the occurrence of ALS was also found. Moreover, a possible anticipation effect, with a mean age of onset some 20 years lower than the mean age of onset of ALS in prospective epidemiological studies was observed (Traynor *et al*., 1999; Chiò *et al*., 2002). Interestingly, when considering the whole series of 18 professional players who developed ALS during the study period, the mean age of onset was 51.2 years (SD 12.4, range 33–74), >10 years lower than expected. Considering the clinical characteristics of the five cases, there was a significant excess of bulbar onset compared with the data of the two Italian ALS registers. The mean duration of ALS was lower than expected for young onset cases, but within the range of classical ALS (Chiò *et al*., 2002).

The possibility of a 'false cluster' should be considered. According to the definition given by Armon *et al*. (1991), the observed SMR should be corrected for 'implicit multiple comparisons', i.e. identified clusters in small communities may merely represent random concatenations noticed by larger groups of communities capable of reporting clusters. Considering the professional sports in Italy, the total number of possible comparisons does not exceed 30; therefore, even after the proposed correction, the lower limit of SMR confidence interval would largely exceed 1. Moreover, all other requirements for a correct evaluation of an identified cluster (incident case definition, population at risk determination, a long period of observation, diagnosis and case ascertainment) (Armon *et al*., 1991) have been met using a highly conservative design.

Our findings seem to indicate that a factor (or more factors acting together) related to professional football in Italy has a role in determining an increased risk of ALS. The exposure(s) that may have caused or triggered ALS in this cohort remain unknown. Four hypotheses can be proposed:

(i) ALS in football players is related simply to participation in sport or to heavy physical exercise, and therefore is not specifically linked to football;

(ii) ALS is related to traumas or microtraumas, perhaps football-specific, i.e. heading the ball, repeated traumas involving the legs, or traumas specifically related to football training or playing such as muscle or tendon straining or tearing;

(iii) ALS is related to either the use of illegal, toxic substances assumed to improve athletic performances or to the use of therapeutic drugs employed in doses in excess of or for a longer period than indicated by drug companies or regulatory authorities; or

(iv) ALS is related to environmental toxins such as fertilizers or herbicides used on football fields, to which football players have an extended exposure.

Considering the inconsistent results of case control studies which have evaluated this relationship, the possible non-specific effect of sport participation or strenuous exercise on ALS development in the football cohort is unlikely. Moreover, at best, a 1.5–2 times increased risk was found (Longstreth *et al*., 1998; Scarmeas *et al*., 2002)—considerably lower than the SMR observed in our series. In addition, studies performed on transgenic mice overexpressing the mutant superoxide dismutase gene 1 (SOD1)—the animal model for ALS—gave contradictory findings (Veldink *et al*., 2003; Mahoney *et al*., 2004).

The effect of football-specific traumas/microtraumas cannot be ruled out since trauma is an alleged risk factor for ALS (Strickland *et al*., 1996). However, currently there are few, if any, data supporting the relationship between mechanical traumas and ALS (Kurland *et al*., 1992; Armon, 2003). Interestingly, three out of five cases in our series had a bulbar onset of ALS, a site of onset that could be linked to heading the ball—a type of trauma relatively football-specific (Piazza *et al*., 2004)—and which has been related to poorer results in cognitive tests in football players (Matser *et al*., 2001).

The suggestion that one or more toxic substances may act as triggers for ALS is not new, although no specific substance has yet been identified, even in the ALS high incidence foci of the western Pacific (Mitchell, 2000). In our series, the young age of onset of cases may support the hypothesis that a noxious substance may have triggered ALS prematurely, perhaps in individuals with a genetic predisposition due to particular polymorphisms of xenobiotic detoxifying genes.

The understanding of the cause of ALS remains a crucial step towards the goal of developing an effective therapy for this disorder. According to our findings, prospective studies of active professional football player cohorts, including an analysis of their environmental and toxic exposures, may represent an invaluable opportunity to uncover the mechanisms underlying ALS pathogenesis.

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