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Amyotrophic Lateral Sclerosis and soccer: an internet survey of 29 Italian players

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Abstract

Objectives. Previous epidemiological studies reported a significantly higher risk of Amyotrophic Lateral Sclerosis (ALS) in Italian male soccer players. As a consequence, sports newspapers and news agencies focused on this issue and spread the news of 51 male soccer players with a reported diagnosis of ALS.

Design. We searched news on male Italian national soccer players with a reported diagnosis of ALS quoted from January 1, 1950 to July 31, 2016 in at least two Internet web sites or in books by journalists.

Results. A total of 39 male soccer players with a reported diagnosis of ALS were identified. Subjects were born from 1905 to 1973, 32 were currently deceased, 6 were still living, while the status of 1 player was unknown. All gathered information was available for 29 soccer players. The group had a mean age at diagnosis of 45.3 ± 12.2 years, a mean age at onset of symptoms of 46.4 ± 12.1 years, and a mean age at death of 50.9 ± 12.3 years. A significant inverse correlation between year of birth and age at onset of symptoms was observed, with a younger age at onset of symptoms in soccer players born in more recent years ($r = -0.65$, $p < 0.01$).

Conclusions. Italian male soccer players with a reported diagnosis of ALS have a significantly younger age at diagnosis when compared to other European patients with ALS. Results support a possible relationship between soccer and the risk of ALS. We believe that further research is urgently needed in this field.

Key words

- Amyotrophic Lateral Sclerosis
- soccer
- sport

INTRODUCTION

Three epidemiological cohort studies have been published during the last years on the risk of Amyotrophic Lateral Sclerosis (ALS) in Italian soccer players [1-3]. The first study enrolled a cohort of 24 000 male Italian soccer players that were active in three top leagues (A, B and C) between 1960 and 1996, and observed a 12-times higher standardized proportionate mortality ratio (SPMR) for ALS (8 observed cases *vs* 0.69 expected cases; SPMR = 1158, 95% CI 672-1992) [1]. Moreover, age at death in 6 subjects (out of 8) was lower than 59 years [1]. The second study reported a 18-times higher standardized mortality rate (SMR) for ALS in 5389 Italian male professional soccer players that were active between 1975 and 2003 in the A and B leagues (4 observed cases *vs* 0.2 expected cases; SMR = 18.18, 95% CI 5.00-46.55) [2]. The last paper enrolled a cohort of 7325 Italian male professional soccer players that were active between 1970 and 2001 in the A and B leagues, and followed up the cohort up to December 31, 2006 [3], observing a 6.5-times higher SMR for ALS (8 observed cases *vs* 1.24 expected cases; SMR = 6.45; 95% CI 2.78-12.70) [3]. Five out of the 8 observed cases had bulbar symptoms at onset [3], and all the 8 cases were sporadic [3]. Moreover, a higher risk of ALS was reported in players with a career lasting more than 5 years, in athletes playing as midfielders, and in players engaged after 1980. A younger age at onset (mean 41.6 years) was also reported [3]. All the studies by Belli *et al*. and by Chiò *et al*. were designed and carried out within the framework of an inquiry by an Italian Public Prosecutor aimed at assessing the possible long term effects of doping [1, 3].

These epidemiological studies carried out on the co-

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hort of Italian soccer players led to a methodological discussion on the most appropriate way to calculate the number of expected cases. However, available epidemiological evidence still supports this association [4-7].

The above mentioned studies had a wide impact within the Italian sports and scientific community. As a consequence, sports newspapers and news agencies released the news of 51 male soccer players (either deceased or alive) with a reported diagnosis of ALS [8, 9].

This survey aimed at collecting all available information on male Italian national soccer players for which a ALS diagnosis was cited either on the Internet or in journalists' books with the objective of describing the clinical and professional characteristics of this specific group of subjects.

MATERIALS AND METHODS

All information on male Italian soccer players reported as having a diagnosis of ALS in at least two Internet web sites (Wikipedia, sports newspapers, news media and sports related websites) or in journalists' books published between January 1, 1950 and July 31, 2016 were retrieved. The following key words were used either individually or in combination: "soccer player name", "Italian soccer players", "Amyotrophic Lateral Sclerosis","ALS", "motor neuron disease", "neurological disease", "Lou Gehrig disease" "death". For each subject the following information was also searched: date of birth, date of death (if not alive), age at diagnosis, age at onset of symptoms, duration of their career as soccer players and role, league(s) and/or team(s) in which they played. The age at diagnosis if missing, was calculated as the age at death minus 3 years, or as the age at onset of symptoms plus 1 year (when at least one of these two information data were available). In case for a subjects the age at onset of symptoms was missing, it was calculated being either four years prior the age at death, or one year prior the age at diagnosis (when at least one of these two information data were available) [10]. The choice of these cutoffs refers to a paper published by Czaplinski *et al*. that estimated a median survival of 4.32 years and about 1 year of diagnostic delay form symptoms onset in a group of patients with ALS diagnosed between 1999 and 2004 [10]. Moreover, a sensitivity analysis was carried out including only actually collected/non-imputed data.

Data are expressed as means (± SD) or medians (and range) for continuous variables, and as proportions for categorical variables.

For continuous variables, the Mann-Whitney-U-test was used to compare medians.

A correlation analysis was performed using the Pearson index to assess the association between age at onset of symptoms and year of birth. All statistical analyses were carried out using the SPSS software (version n. 22). P values < 0.05 were considered as statistically significant.

All data used in our survey were available for free online. A detailed list of the websites and books consulted, and of the information gathered on all the Italian professional soccer players with a diagnosis of ALS are available upon request. The study did not receive any specific funding, and was carried out within the current institutional research activities on the possible association between soccer and ALS.

RESULTS

A total of 54 male Italian soccer players with a reported diagnosis of ALS were identified through internet web. Further research, however, showed that 12 of these players actually had a non-neurological disease, 3 had other neurological diseases, and 39 had an actual diagnosis of ALS *(Figure 1)*. The 39 subjects with a diagnosis of ALS were born between 1905 and 1973, 32 of them were deceased, 6 were still living, while the status of 1 player was unknown. A total of 33 of these athletes played at least for 1 year in one of the top leagues (A, B and C), while 6 of them had only played in amateur leagues. As previous studies focused on professional players, we considered only the athletes that played in the top leagues (A, B or C), and excluded the amateur players from the analyses [1-3]. A total 33 players was therefore considered in the descriptive analyses. Age at diagnosis, age at onset of symptoms, and age at death (if not alive) were available for 10, 15 and 27 of the 33 subjects, respectively. None of these data were as available for 4 players, that were, thus, excluded. *Table 1* reports all the information on the 29 soccer players included in the descriptive analyses. Mean age at diagnosis was 46.4 ± 12.2 years, mean age at onset of symptoms was 45.3 ± 12.3 years, mean age at death was 50.9 ± 12.3 years, and mean length of the career in the

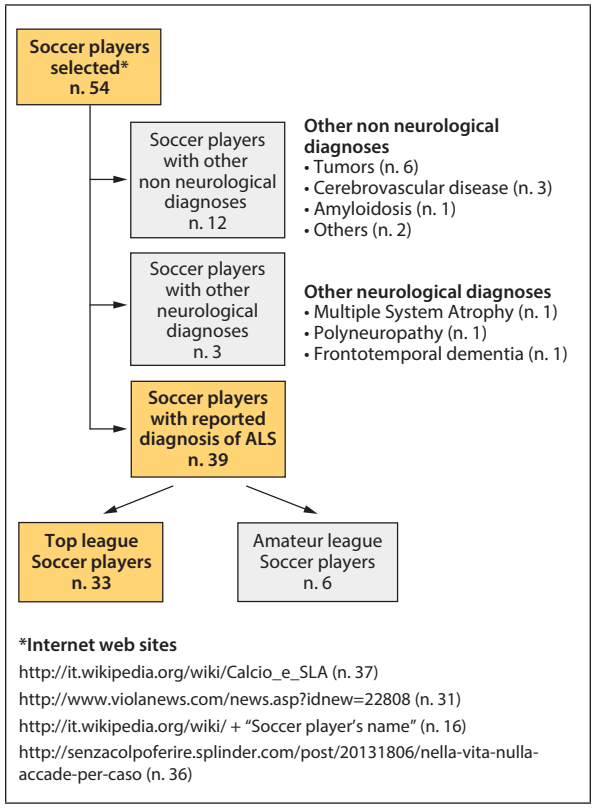

Figure 1
Flow chart of the Italian soccer players identified.

Table 1
List of the 29 Italian soccer players included in the descriptive analyses

ID	Vital status*	Cohort of birth	Soccer position	Top League	Period of play	Age at onset (years)	Duration of the disease (years)
1	D	≤ 1940	Midfielder	A	48-64	37*	6
2	D	≤ 1940	Goalkeeper	A	47-62	58*	2
3	D	≤ 1940	Defender	A	50-69	63*	2
4	D	≤ 1940	Midfielder	A	19-43	76	3
5	D	≤ 1940	Midfielder	A	42-53	37*	4
6	D	≤ 1940	Forward	A	56-63	40*	4
7	D	≤ 1940	Midfielder	B	60-71	37*	4
8	D	≤ 1940	Goalkeeper	A	54-69	55*	4
9	D	≤ 1940	Goalkeeper	A	61-62	64*	5
10	D	1941-1960	Forward	C	66-70	59	2
11	D	1941-1960	Defender	A	78-97	39	3
12	D	1941-1960	Forward	B	65-66	51	20
13	D	1941-1960	Midfielder	C	70-72	44*	11
14	D	1941-1960	Midfielder	C	78-94	44	9
15	D	1941-1960	-	A	-	56*	4
16	D	1941-1960	Midfielder	A	65-83	59	3
17	D	1941-1960	Midfielder	A	64-83	36*	4
18	D	1941-1960	Forward	B	60-70	55	2
19	A	1941-1960	-	C	-	48*	9
20	D	> 1960	Forward	A	81-96	39	10
21	D	> 1960	Defender	C	79-94	40	10
22	A	> 1960	Forward	A	90-94	36	11
23	D	> 1960	Defender	A	80-89	35	3
24	D	> 1960	Midfielder	C	93-99	24	7
25	D	> 1960	Midfielder	C	83-92	29*	10
26	D	> 1960	Midfielder	C	81-88	33	2
27	D	> 1960	Defender	C	-	41*	3
28	D	> 1960	Defender	B	79-98	49	4
29	D	> 1960	Defender	C	-	31	5

*D: deceased; A: alive
* values attributed

top leagues (A, B and C) was 12.5 ± 6.7 *(Table 2)*. The sensitivity analysis, excluding imputed data, showed no statistically significant differences neither for mean age at diagnosis (n = 10; 43.4 ± 11.8 years) nor for mean age at onset of symptoms (n = 15; 44.1 ± 13.5 years).

A total of 3 of the included athletes played as goalkeepers, 7 as defenders, 11 as midfielders, and 6 as forwards, while for 2 players the information was missing. A total of 6 players resulted as having played in the Como team for the longest time, 4 in Milan, 4 in Pisa, 4 in Fiorentina, and 4 in Inter.

We calculated the frequency of incident cases of ALS, and compared it with the results from a large study based on data from European population-based ALS registries [11] *(Figure 2)*. *Figure 2* reports the comparison between the two set of data, and shows a peculiar pattern of distribution for age at diagnosis in Italian male soccer player when compared to the incident European male cases included in the population-based registries [11].

No statistically significant association was observed between role and median age at onset of symptoms (p = 0.13), nor between role and length of the career in the top leagues (p = 0.18), while a statistically significant association was observed between the three cohorts of birth and the age at onset of symptoms (p = 0.006) *(Table 3)*. No statistically significant association was found between the three cohorts of birth and the length of the career in the top leagues (p = 0.75) *(Table 3)*.

An inverse statistically significant correlation was observed between year at birth and age at onset of symptoms, with a younger age at onset of symptoms in players that were born in more recent years (r = -0.65, p < 0.01). No statistically significant correlation was ob-

Table 2
Characteristic of the 29 Italian soccer players included in the descriptive analyses

	N.
Total	**29**
Dead	27
Alive	2
	Mean ± SD; Median (*range*)
Age at onset (years)	45.3 ± 12.3; 41 (24-76)
Age at diagnosis (years)	46.4 ± 12.2; 42 (26-77)
Length of disease (years)	5.7 ± 4.1; 4 (2-20)
Age at death (years)	50.9 ± 12.3; 50 (31-79)
Length of the career	12.5 ± 6.7; 12 (2-25)

served between age at onset symptoms and length of the career in the top leagues (p = 0.24).

DISCUSSION

This survey confirms the clinical and occupational results observed in Italian soccer players included in a cohort study based on 8 reported cases [3]. In particular, the soccer players identified as having ALS in the present study resulted as having a distinctly younger age at diagnosis when compared to other European patients with ALS from the general population [10]. This anticipation of the diagnosis appears to be even more marked in more recent years (after 1980), even though players with ALS who were born after 1960 and had an age at onset of symptoms > 55 years could not be fully observed, thus possibly causing a selection bias *(Table 3)*. Moreover, our results showed that midfielders seem to have a higher risk when compared to athletes playing in other roles.

One limitation of our survey is that all cases of ALS were identified through Internet websites and books, and not from clinical records. This did not allow us to confirm the diagnosis, nor to gather further information on clinical records or on a possible familiarity for ALS. Most of the cases of ALS included in our study, though, were famous soccer players, thus it can be considered as highly improbable that any adjustment of the diagnosis would not have been made public. However, we identified 12 players who had no neurological diseases but were mistakenly reported as having ALS by sports newspapers and press agencies *(Figure 1)*. The age at diagnosis was calculated as the age at death minus 3 years.

This restrictive decision could have only slightly influenced the observed younger age at diagnosis reported in *Figure 2*.

Acquiring information from the Internet for scientific purposes is becoming increasingly easier and thus potentially useful to test some hypotheses. A study on football as a potential risk factor for ALS was performed on National Football League players in the United States using the Internet as a source on information [12]. The study found that 8 out of the 3891 players who were active or debuted after 1960 were diagnosed with ALS, resulting in a prevalence of 206 per 100 000, which means a prevalence rate 40-times higher than the one reported in the general US population (5 per 100 000) [12]. A further study, by Wicks *et al.*, used information shared online by patients with ALS who experimented a treatment with lithium carbonate, and showed that the Internet can be an extremely useful tool to accelerate clinical discovery and assess the effectiveness of drugs already in use [13].

A further result emerging from our survey is the difference between the number of professional soccer players identified as having ALS on the Internet and the number of those included in the previously mentioned epidemiological studies [1-3]. One of the reasons for this observation could be that ALS could be reported only as intermediate and final cause of death, and not as the initial one. Other reasons for this discrepancy could

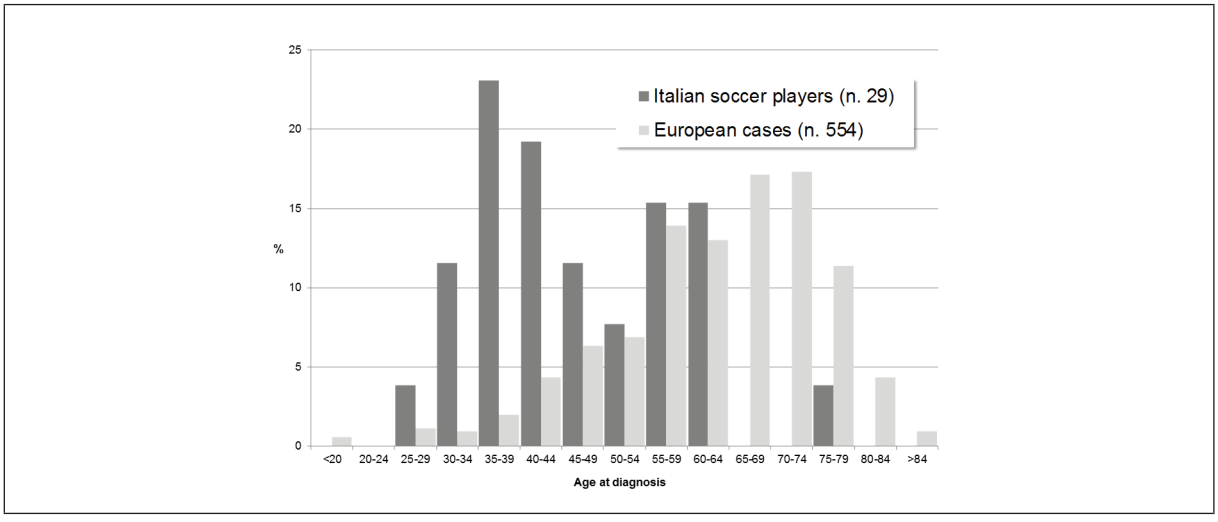

Figure 2
Comparison between the frequency of incident cases of ALS in the Italian male soccer players and in the European population-based ALS registries.

Table 3
Association between role and cohorts of birth with age at onset of symptoms and years of play

	N.	Median age at onset of symptoms (range)	Median years of play in the top leagues (range)
Role^		ns	ns
Goalkeeper	3	59 (56-65)	16 (2-16)
Defender	7	41 (32-64)	20 (10-21)
Midfielder	11	38 (26-77)	12 (3-25)
Forward	6	47 (37-60)	7 (2-16)
Cohorts of birth		p = 0.006	ns
≤ 1940	9	56 (38-77)	16 (2-25)
1941-1960	10	51 (37-60)	14 (2-21)
> 1960	10	37 (26-50)	10 (5-20)

^ two roles were not reported.

be the different time period of the three studies (1960-1996, 1970-2003, 1971-2006 years) [1-3], the decision of including or excluding athletes that only played in the C league (6 of the cases included in our survey who had only played in C), the accuracy of the available diagnosis for incident cases, or the impossibility of obtaining a complete list of soccer players from the Italian Soccer League. An additional reason could be that, for privacy reasons, some soccer players may not have spread the news of their clinical conditions.

Several hypotheses were raised to explain the higher frequency of ALS among Italian soccer players. One of the hypotheses linked the increased risk to an excessive consumption of dietary supplements containing branched chain amino acids (BCAAs) [14-18], of chronic anti-inflammatory drugs [19], or of anabolic/androgenic steroids [22]. Other studies focused on head traumas [20, 21], exposure to pesticides and/or herbicides [23], or to toxins produced by cyanobacteria [24]. The probability that the younger onset of ALS could be related to an environmental factor seems to be very high in soccer players with a genetic predisposition to the disease. A recent study on the heritability of ALS reported that environmental factors and genetic factors appear to be nearly equally relevant in triggering the onset of ALS [25].

One further hypothesis to explain the higher frequency of ALS in Italian soccer players suggests that this tactical role requires a strenuous physical exercise, occasionally in anaerobic conditions, thus possibly resulting in hypoxia at a neuronal tissue level. As reported in a previously published study, conditions typically leading to intermittent hypoxia might be a risk factor for ALS in subjects who are genetically predisposed to an abnormal response to hypoxia [26]. A possible explanation for the younger age at diagnosis in players born in more recent years and for the higher risk observed in top leagues, could be a progressive increase in more recent years of the frequency of all mentioned environmental factors, in particular in the top leagues, and/or a higher exposure of this cohort to some unknown factors. Moreover, our results showed a higher risk only in few teams, and this finding should be further confirmed.

Currently available clinical and epidemiological evidence supports a possible correlation between the specific occupational environment of soccer and the risk of ALS [1-3, 27-29].

CONCLUSIONS

We believe that further research is urgently needed to explain the reasons for this unexpected and still unintelligible ALS cluster among Italian professional soccer players. Soccer players are a small proportion of all Italian cases of ALS (about 0.25% of prevalent cases), but this subgroup can be considered as a unique opportunity to understand the causes of this devastating neurological disorder. To this purpose, officers of the judicial system and the entire scientific community should find a fruitful way to cooperate in understanding the reasons for this striking singularity [30].

Specifically, to clarify the specific risk of ALS in each subgroup, a cohort mortality study should be carried out on four Italian soccer player groups, namely male professional players, male amateur leagues players, male active players in soccer five, and female professional and amateur active players. This information could be extremely useful to better explain the higher risk of ALS reported in the scientific literature. Additionally, a nested case-control study could also be carried out to investigate all currently known risk factors for ALS, further characterize the clinical aspects, such as type of ALS, familiarity, age at symptom-onset, and of the occupational aspects, such as trauma, drugs use, length of the career, including as an amateur, of all ALS soccer players (both deceased and alive) should be performed. A definition of the genetic risk of ALS among soccer players could also be very useful. Moreover, further epidemiological studies, with adequate sample size, should be carried out on non-Italian professional soccer players, and on other cohorts of professional athletes.

In conclusion we would like to reiterate that our study is based on 54 football players identified by the sources cited in the methodology and that all subjects included in our study are male because epidemiological and clinical studies [1-3, 27-29] are based only on the male professional football.

Acknowledgments

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Conflict of interest statement

All authors declare that they have no conflict of interest.

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