American Journal of Epidemiology
Published by the Johns Hopkins Bloomberg School of Public Health 2007.

Vol. 166, No. 7
DOI: 10.1093/aje/kwm153
Advance Access publication July 19, 2007

Original Contribution

Head Injury and Amyotrophic Lateral Sclerosis

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Received for publication December 28, 2006; accepted for publication April 23, 2007.

Recent data showed that soccer players in Italy had an unusually high risk of amyotrophic lateral sclerosis (ALS) and that repeated head trauma might have contributed to this increase. The authors examined whether head injury was related to ALS risk in a case-control study of 109 New England ALS cases diagnosed in 1993–1996 and 255 matched controls. They also conducted a meta-analysis of the published literature. Overall, ever having experienced a head injury was nonsignificantly associated with a higher ALS risk. When compared with persons without a head injury, a statistically significant ALS risk elevation was found for participants with more than one head injury (odds ratio (OR) = 3.1, 95 percent confidence interval (CI): 1.2, 8.1) and patients who had had a head injury during the past 10 years (OR = 3.2, 95 percent CI: 1.0, 10.2). For participants who had had multiple head injuries with the latest occurring in the past 10 years, risk was elevated more than 11-fold. The meta-analysis also indicated a moderately elevated risk of ALS among persons with previous head injuries (OR = 1.7, 95 percent CI: 1.3, 2.2). In this study population, physical injuries to other body parts, including the trunk, arms, or legs, were not related to ALS risk. These data support the notion that head injury may increase the risk of ALS.

amyotrophic lateral sclerosis; craniocerebral trauma; head injuries, closed; head injuries, penetrating

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio; SOD1, superoxide dismutase 1.

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by the progressive death of both upper and lower motor neurons. The incidence of ALS is very low in the general population (1) but sharply increases after age 40 years and peaks around age 75. ALS patients have a high mortality rate. More than 50 percent die within 3 years after the diagnosis (1, 2). Mutations in the superoxide dismutase 1 (*SOD1*) gene are responsible for approximately 20 percent of the familial cases, or 1–2 percent of the overall ALS patient population, but for most sporadic cases the causes are not known.

Clinical observations and case-control studies have suggested that physical trauma may be associated with a higher risk of ALS, but the evidence is far from conclusive (3). Recently, two reports showed that ALS incidence and mortality were unusually high among professional soccer players in Italy (4, 5). One hypothesis proposed to explain these findings is that repeated neurologic trauma associated with heading the ball may increase the risk of ALS (6). Therefore, we examined the relation between head injury, as well as injuries at other body sites, and risk of ALS in a case-control study. We also conducted a meta-analysis of studies in the published literature to examine the relation between head injury and ALS.

MATERIALS AND METHODS

Details of the study design have been published previously (7–9). Briefly, ALS patients were recruited between

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1993 and 1996 from two major referral centers in New England: the Neuromuscular Research Unit at Tufts-New England Medical Center and the Neurophysiology Laboratory at Brigham and Women's Hospital, both located in Boston, Massachusetts. Sequential ALS patients diagnosed according to the standard criteria of the World Federation of Neurology (10) were considered eligible for the study if they had been diagnosed within the previous 2 years, lived in New England for at least 50 percent of the year, spoke English, and were mentally competent. Of the 154 eligible cases, two could not be contacted and 42 declined (seven because of sickness, 15 because of travel difficulties, and 20 for other reasons), leaving a total of 110 patients in our study.

Population controls were selected using the same eligibility criteria, plus the absence of a diagnosis of dementia, Parkinsonism, neuropathy, postpolio syndrome, ALS, or other motor neuron diseases. Controls were frequency-matched to cases by age (30–55, 56–65, and 66–80 years), gender, and telephone area code (as a surrogate for region within New England), at a ratio of 3:1 for the Boston area and 2:1 for other areas in New England. These controls were selected through random telephone screening based on a modified Waksberg method with two-stage sampling. A total of 354 eligible controls were contacted, and 270 (76 percent) were enrolled in the study; 256 completed the entire questionnaire.

All study participants provided written informed consent. The study protocol was approved by the institutional review boards of the National Institute of Environmental Health Sciences, Tufts-New England Medical Center, and Brigham and Women's Hospital.

Exposure assessment

Information on demographic and lifestyle characteristics and on residential and occupational histories was collected using a structured questionnaire administered by trained interviewers. Cases were interviewed in person and controls by telephone. All participants were asked whether they had ever been injured so severely that they required medical attention—for example, while playing a sport or being involved in a fight or an accident. If they answered yes, they were asked how many times they had been injured and at what ages the injuries had occurred. For up to three incidents, participants were asked whether the injury had involved the head, trunk, right arm, left arm, right leg, or left leg. During the interview, they were also asked to provide other exposure information, including cigarette smoking history and highest level of education.

Statistical analysis

Physical injury variables were categorized before data analyses. The reference date was defined as the date of diagnosis for cases and 2 years before the interview date for controls, as all cases were interviewed within 2 years of their first diagnosis. One case and one control reported inconsistent information across injury-related questions and therefore were classified as having missing data; this left us with an analytic sample of 109 cases and 255 controls. Exposures were first defined as "ever versus never" with regard to overall injury as well as injuries occurring at specific body sites. Furthermore, for each body site, we defined exposures according to number of injuries (0 (never injured), 1, or >1), years since last injury (0 (never injured), >30, 11–30, or ≤10), age at last injury (never injured, <30 years, 30–39 years, or ≥40 years), and whether a given incident had involved more than one body site (never injured, that particular site only, or that site plus other sites). Odds ratios and 95 percent confidence intervals were calculated from unconditional logistic regression models, first adjusting only for matching factors (10-year age group, gender, and region/area code) and then further adjusting for smoking (ever vs. never) and educational achievement (high school or less vs. more than high school), since both of these variables were related to ALS risk in the study population. To test the robustness of the results, we repeated the analyses after excluding cases and controls who reported a family history of ALS ($n = 8$ and $n = 2$, respectively) or any injuries within 3 years of the reference date ($n = 2$ and $n = 3$, respectively). All statistical analyses were conducted using SAS software (SAS Institute Inc., Cary, North Carolina).

Finally, we conducted a meta-analysis on the relation between head injury and risk of ALS. We identified eight papers published since 1980 on head injury and ALS by searching MEDLINE and the reference sections of previous publications. All of the studies but one (11) were included in the meta-analysis, together with the current study. The study by Gresham et al. (11) was excluded because the numbers were not consistent across the text and a risk estimate could not be calculated. For published articles that did not provide a summary estimate, we calculated odds ratios and 95 percent confidence intervals when possible, using standard formulas. For individually matched case-control studies, the data were often presented in a way that makes matched risk estimate calculations impossible, and therefore unmatched odds ratios and 95 percent confidence intervals were calculated instead. Except in the current study, risk estimates were not adjusted for potential confounders. Because there was no statistical heterogeneity among the risk estimates across studies (p for heterogeneity $= 0.1$), the summary odds ratio was obtained with a fixed-effects model, using STATA software (version 8; Stata Corporation, College Station, Texas).

RESULTS

The population characteristics of cases and controls have been published previously (7–9) and thus are not presented here. The average age at diagnosis for cases was 58.3 years. Diagnosis was made, on average, 14.3 months after the self-reported onset of symptoms. Overall, 27 (24.8 percent) of the patients had a bulbar onset and 82 (75.2 percent) had an extremity onset. Among controls, approximately 45 percent reported an experience of severe physical injury in their lifetime that required medical attention. These injuries were most likely to have occurred in the legs (20.9 percent),

TABLE 1. Association of amyotrophic lateral sclerosis with physical injury in a case-control study conducted in New England, 1993–1996

Injury site	Cases (%) ($n = 109$)	Controls (%) ($n = 255$)	Model 1*		Model 2†	
			OR‡	95% CI‡	OR	95% CI
Any site(s)						
No	53.2	54.9	1.0		1.0	
Yes	46.8	45.1	1.1	0.7, 1.8	1.2	0.7, 1.9
Head						
No	78.0	83.5	1.0		1.0	
Yes	22.0	16.5	1.5	0.8, 2.7	1.4	0.8, 2.6
Trunk						
No	89.9	88.6	1.0		1.0	
Yes	10.1	11.4	0.9	0.4, 1.8	0.9	0.4, 1.9
Arm						
No	88.1	80.8	1.0		1.0	
Yes	11.9	19.2	0.6	0.3, 1.1	0.6	0.3, 1.1
Leg§						
No	79.8	79.1	1.0		1.0	
Yes	20.2	20.9	1.0	0.6, 1.8	1.0	0.6, 1.8

* Results were adjusted for matching factors (age, gender, and region/area code within New England).
† In addition to the above factors, results were adjusted for education and smoking.
‡ OR, odds ratio; CI, confidence interval.
§ One control had missing information on leg injury.

followed by the arms (19.2 percent), head (16.5 percent), and trunk (11.4 percent) (table 1).

Overall, ever having had an injury was not related to a higher risk of ALS (table 1). Among individual body sites, only head injury tended to be associated with a higher risk of ALS (odds ratio (OR) = 1.4, 95 percent confidence interval (CI): 0.8, 2.6), but the association was not statistically significant. Detailed analyses (table 2) indicated that having experienced repeated head injuries or having been injured within the 10 years before diagnosis was associated with a more than threefold higher risk of ALS (OR = 3.1 (95 percent CI: 1.2, 8.1) and OR = 3.2 (95 percent CI: 1.0, 10.2), respectively). A post-hoc exploratory analysis based on small numbers showed that persons who had experienced repeated head injuries with the latest occurring in the past 10 years had more than an 11-fold higher ALS risk than those without a head injury. Finally, cases with head injuries were more likely to have a bulbar onset (33.3 percent vs. 22.4 percent; $p = 0.3$) and an earlier age of diagnosis than cases without previous head injuries (54.0 years vs. 59.5 years; $p = 0.05$). Interestingly, three of the four cases (75 percent) with repeated head injuries with the latest occurring in the 10 years before diagnosis had a bulbar onset, and despite the small sample size, the proportion was significantly greater than that among cases without head injuries (Fisher's exact test: $p < 0.05$). The overall results on head injury and ALS were essentially unchanged when we excluded participants with a family history of ALS or with a head injury that occurred within 3 years of the reference date. The only change was that the odds ratio for head injury within the past 10 years was even higher (OR = 5.6, 95 percent CI: 1.3, 24.4) in the 3-year-lagged analysis.

In contrast to head injury, no other injuries were related to a higher risk of ALS. The odds of having ALS were lower among persons with a history of arm injury. However, further analyses of arm injuries and injuries at any other body site did not reveal consistent patterns of association.

Most of the identified studies on physical trauma and ALS were published in the 1980s or early 1990s. In these studies, head injury was often ascertained along with injuries at other body sites, and the definition of head injury varied, mostly without any specifics (table 3). The results also varied across studies, with odds ratios ranging from 0.8 to 5.6 (figure 1). Nevertheless, the meta-analysis revealed a significant association between head injury and risk of ALS: Compared with persons without head injury, the risk of ALS was 1.7 times (95 percent CI: 1.3, 2.2; $p < 0.001$) higher among persons with head injuries. Further analysis was impossible, since nearly all studies lacked sufficient details.

DISCUSSION

ALS is the most common motor neuron disease. Its causes are largely unknown, although they are likely to involve environmental components. In this case-control study, head injury was associated with an elevated risk of ALS, particularly for recent repeated head injuries. Though it was based on small numbers, the odds ratio for ALS was 11

TABLE 2. Association of amyotrophic lateral sclerosis with head injury in a case-control study conducted in New England, 1993–1996

	Cases (%) ($n = 109$)	Controls (%) ($n = 255$)	Model 1*		Model 2†	
			OR‡	95% CI‡	OR	95% CI
No. of head injuries						
0 (never injured)	78.0	83.5	1.0		1.0	
1	11.9	12.5	1.1	0.5, 2.2	0.9	0.4, 2.0
>1	10.1	3.9	2.9	1.1, 7.6	3.1	1.2, 8.1
Years since last injury						
0 (never injured)	78.0	83.5	1.0		1.0	
>30	4.6	5.9	0.9	0.3, 2.7	0.9	0.3, 2.7
11–30	10.1	8.2	1.4	0.6, 3.1	1.2	0.5, 2.9
≤10	7.3	2.4	3.2	1.0, 9.8	3.2	1.0, 10.2
No. of head injuries and years since last injury						
0 (never injured)	78.0	83.5	1.0		1.0	
1 injury at any time	11.9	12.5	1.1	0.5, 2.2	0.9	0.4, 1.9
>1 injury, with the last one >10 years before	6.4	3.5	2.2	0.7, 6.4	2.2	0.7, 6.5
>1 injury, with the last one ≤10 years before	3.7	0.4	9.2	0.9, 88.3	11.3	1.1, 114.3
Age (years) at last injury						
Never injured	78.0	83.5	1.0		1.0	
<30	11.9	12.2	1.2	0.6, 2.4	1.1	0.5, 2.3
30–40	2.8	2.0	1.5	0.3, 6.5	1.4	0.3, 6.7
>40	7.3	2.4	2.7	0.9, 8.3	2.8	0.9, 8.9
Involvement of other body sites in the same incident						
Never injured	78.0	83.5	1.0		1.0	
Head only	14.7	12.2	1.4	0.7, 2.7	1.4	0.7, 2.9
Head with other body sites	7.3	4.3	1.8	0.7, 4.9	1.4	0.5, 3.8

* Results were adjusted for matching factors (age, gender, and region/area code within New England).

† In addition to the above factors, results were adjusted for education and smoking.

‡ OR, odds ratio; CI, confidence interval.

times higher among persons who had had multiple head injuries with the latest occurring in the 10 years prior to diagnosis. Consistent with the recent reports on ALS among Italian soccer players (4, 5), ALS cases with a previous head injury were more likely to have an early and bulbar onset. The results of the meta-analysis further support a link between head injury and ALS.

These findings are consistent with the hypothesis that head injury increases ALS risk. An alternative explanation is that the preclinical symptoms of ALS might have predisposed patients to a higher risk of physical injury. Although we could not exclude this possibility, its plausibility is weakened by the lack of association between ALS and overall injury or injuries to other parts of the body, which were assessed along with head injury in the same structured questionnaire, as well as by the fact that a slightly stronger association was found when injuries occurring within 3 years of the reference date were excluded from the analysis. By the same token, significant recall bias is not a likely explanation for our results, since antecedent reports more frequently implicated injuries involving the shoulders and arms (12, 13)—findings which might have been more publicized among patients.

Recent data showed that ALS mortality among Italian professional soccer players was approximately 12-fold higher than expected (4), while mortality from other causes was generally lower than or comparable to that of the general population. This finding was subsequently confirmed by an incidence study carried out among 7,325 Italian professional soccer players who had played between 1970 and 2001 (5). The incidence of ALS was 6.5 times higher than expected, and cases were clinically characterized by early onset and bulbar involvement at diagnosis. Although both analyses were based on small numbers, the consistency of

TABLE 3. Results of published studies conducted since 1980 on head injury in relation to risk of amyotrophic lateral sclerosis

Authors and year (ref. no.)	Study location	Study design	Study population	Exposure assessment	Results
Kurtzke and Beebe, 1980 (25)	United States	Case-control	504 deceased veterans with ALS* and 504 matched veteran controls	Military record abstraction; head injury was not specifically defined.	OR*,†,‡ = 1.0 (95% CI*: 0.1, 7.1)
Kondo and Tsubaki, 1981 (26)	Japan	Case-control	712 deceased MND* cases and 637 spouse controls	In-person interview; head injury was not specifically defined.	Overall OR† = 5.6 (95% CI: 2.5, 12.6)
Deapen and Henderson, 1986 (27)	United States	Case-control	518 volunteer ALS survivors and 518 matched friend controls	Mailed questionnaire; defined as unconsciousness due to external (nonelectrical) trauma; no further details given.	OR = 1.6 (95% CI: 1.0, 2.4)
Gallagher and Sanders, 1987 (13)	United States	Case-control	135 prevalent ALS cases with onset at age <45 years, identified from two patient databases; 85 multiple sclerosis patients as controls	Mailed questionnaire; defined as head or neck injury; no further details given.	OR† = 1.7 (95% CI: 0.8, 3.4)
Gresham et al., 1987 (11)	United States	Case-control	66 cases from existing patient list and 66 matched friend or neighbor controls	Mailed questionnaire; head injury was not specifically defined.	Numbers were not consistent across the text.
Granieri et al., 1988 (28)	Italy	Case-control	72 MND cases primarily from a hospital and 216 matched hospital controls	Medical file abstraction; head injury was not specifically defined.	OR = 1.0 (95% CI: 0.15, 6.81)
Williams et al., 1991 (17)	United States	Retrospective cohort	821 patients with documented head trauma	Medical record review; head trauma with presumed brain injury (concussion or skull fracture)	Standardized morbidity ratio§ = 1.05 (95% CI: 0.027, 5.85)
Chio et al., 1991 (29)	Italy	Case-control	512 hospital MND cases and 512 matched hospital controls, mostly with neurologic conditions	Medical record review; head injury was not specifically defined.	OR = 0.8 (95% CI: 0.2, 1.2)
Current study	United States	Case-control	109 hospital-based cases and 255 frequency-matched community controls	In-person or telephone interview; severe head injury requiring medical attention	Adjusted OR = 1.4 (95% CI: 0.8, 2.6)

* ALS, amyotrophic lateral sclerosis; OR, odds ratio; CI, confidence interval; MND, motor neuron disease.
† An odds ratio was not presented in the original paper, and thus the odds ratio was calculated according to the standard formula.
‡ Matched analysis was impossible.
§ Only one case was identified.

the results and the relatively large effect estimates suggest that the association is not spurious. Several hypotheses have been proposed to explain this association, including vigorous physical activity, the use of performance-enhancing drugs, excessive pesticide exposure, and head trauma (5). The head trauma explanation was particularly interesting, because three of the five patients in the incidence study (5) had a bulbar onset that could be linked to the soccer-specific head trauma and also because some prior data (6) support a link between head trauma and ALS.

An association between physical trauma and ALS has been suggested by many case reports (12, 14) and has been evaluated in several case-control studies (3). In some studies, the nature of the physical trauma was not clearly specified, and in others the definitions varied across studies, from fractures, mechanical injuries, and electric shock to surgery. Not surprisingly, the results from these studies are inconsistent. The studies were further limited by small sample sizes, inadequate exposure assessments, use of convenience controls, and lack of adjustment for potential confounders, and therefore suffered from low statistical power, confounding, and a variety of potential biases (3). Two recent population-based case-control studies both failed to show an association between overall trauma and risk of ALS (15, 16). However, neither study provided specific information on injury site or number of injuries.

Of these previous studies, a few included head injury in the analyses (table 3). All but one were case-control in design and suffered from many of the same limitations as mentioned above. Furthermore, in these studies, rarely were

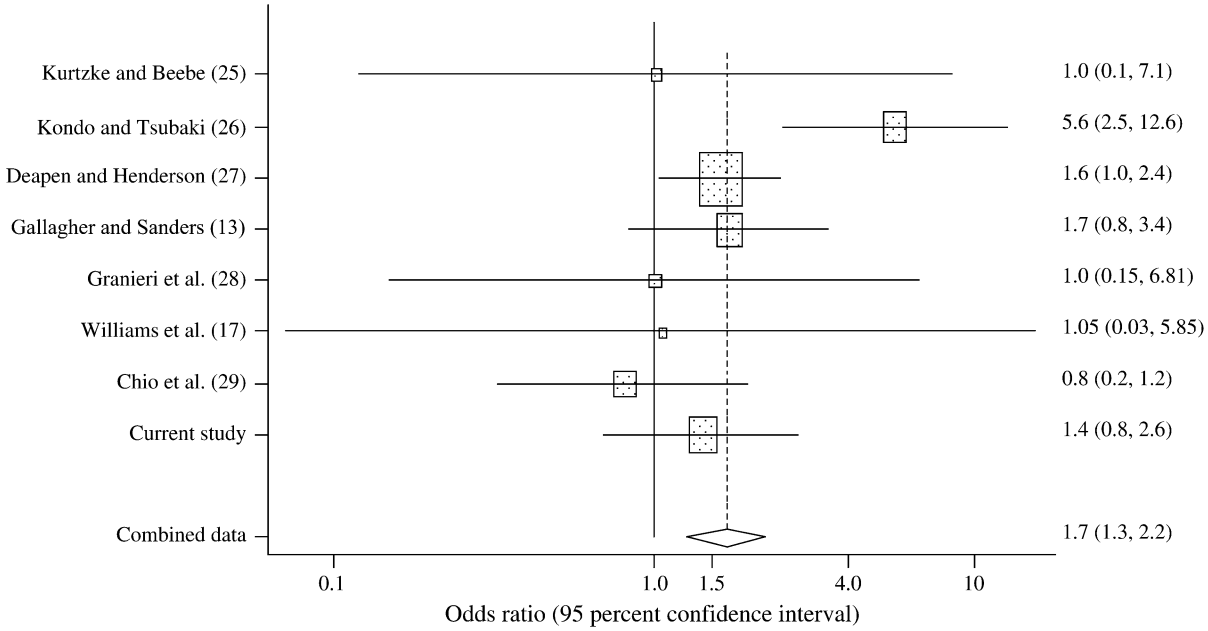

FIGURE 1. Results from a meta-analysis of head injury in relation to risk of amyotrophic lateral sclerosis. The studies included were conducted in the United States, Japan, and Italy, mostly during 1970s and 1980s. Odds ratios and 95% confidence intervals were calculated according to a fixed-effects model. The shaded squares indicate the odds ratios for individual studies (on a log scale). The size of each square is proportional to the percent weight of that study in the meta-analysis; the horizontal lines represent the 95% confidence intervals. The pooled odds ratio and 95% confidence interval are indicated by the diamond. No statistical heterogeneity was found among the risk estimates across individual studies (p for heterogeneity = 0.1).

any specific details on head injury presented. The only prospective study included 821 patients with documented head injury, but only one ALS patient was identified during follow-up (17). Although these studies all suffered from a variety of limitations, the meta-analysis provides preliminary evidence for a positive association between head injury and risk of ALS.

Consistently, the detailed analyses from our study support this link and further suggest that recent repeated injuries may be more etiologically relevant. Recent findings from both clinical observations of asymptomatic *SOD1* mutant carriers (18) and experimental studies of *SOD1* mutant mice (19) suggest that the preclinical motor neuron loss in ALS, like its postdiagnosis clinical course, may be dramatic and aggressive, indicating the importance of recent acute exposure or cumulative exposure as opposed to exposure in the distant past. Our observation of a stronger association with recent repeated head injuries is consistent with this notion.

The mechanisms by which head injury may be implicated in ALS are not known. However, several biologic explanations have been proposed for a possible role of brain injury in other common neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease or dementia (20, 21). These diseases share some clinical, pathologic, and epidemiologic characteristics with ALS and, on rare occasions, occur together (22). Proposed mechanisms include trauma-related neurologic inflammation and microglial activation, disruption of the blood-brain barrier, mitochondrial dysfunction and excessive production of oxidative and nitric radicals, and the accumulation of tau protein (20, 21). While the relevance of these explanations to our observation is unknown, they should be evaluated in future studies of ALS.

This case-control study was one of the better-conducted epidemiologic studies of ALS (23, 24). Compared with previous investigations on head injury and ALS, the current study was better designed, with a clearly defined study population. Furthermore, we collected much more detailed information on head injury and, for the first time, were able to show a clear relation between recent repeated head injury and a higher risk of ALS. Finally, we conducted multivariate analyses to adjust for several potential confounders.

The major limitation of this study is that cases and controls were interviewed by different methods, and therefore potential bias from this source is of concern. Although we cannot exclude this possibility, the lack of associations with injuries at other body sites, such as the arms or shoulders, argues against a substantial bias from this source. As with many of the previous studies, the statistical analyses were limited by small sample sizes. Therefore, we cannot exclude chance as a potential explanation for the findings. Finally, exposure assessment in the current study was not independently validated, and the meaning of severe injury was, to some extent, open to individual interpretation. Furthermore, the definition of head injury as an injury requiring medical attention may limit the generalizability of our findings somewhat. Therefore, future studies should be larger and

investigators should collect more detailed information about each episode of head injury among various populations.

In summary, in line with the recent observations of higher ALS risk among Italian soccer players, we found that recent repeated head injury was related to a higher risk of ALS in an American population. Therefore, a possible role of head injury in ALS etiology should be further evaluated in both human and experimental studies.

ACKNOWLEDGMENTS

This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences.

Conflict of interest: none declared.

REFERENCES

1. Logroscino G, Beghi E, Zoccolella S, et al. Incidence of amyotrophic lateral sclerosis in southern Italy: a population based study. J Neurol Neurosurg Psychiatry 2005;76:1094–8.
2. Millul A, Beghi E, Logroscino G, et al. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. Neuroepidemiology 2005;25:114–19.
3. Kurland LT, Radhakrishnan K, Smith GE, et al. Mechanical trauma as a risk factor in classic amyotrophic lateral sclerosis: lack of epidemiologic evidence. J Neurol Sci 1992;113: 133–43.
4. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? Eur J Epidemiol 2005;20:237–42.
5. Chio A, Benzi G, Dossena M, et al. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain 2005;128:472–6.
6. Piazza O, Siren AL, Ehrenreich H. Soccer, neurotrauma and amyotrophic lateral sclerosis: is there a connection? Curr Med Res Opin 2004;20:505–8.
7. Kamel F, Umbach DM, Munsat TL, et al. Lead exposure and amyotrophic lateral sclerosis. Epidemiology 2002;13:311–19.
8. Kamel F, Umbach DM, Munsat TL, et al. Association of cigarette smoking with amyotrophic lateral sclerosis. Neuroepidemiology 1999;18:194–202.
9. Longnecker MP, Kamel F, Umbach DM, et al. Dietary intake of calcium, magnesium and antioxidants in relation to risk of amyotrophic lateral sclerosis. Neuroepidemiology 2000;19: 210–16.
10. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 1994;124(suppl):96–107.
11. Gresham LS, Molgaard CA, Golbeck AL, et al. Amyotrophic lateral sclerosis and history of skeletal fracture: a case-control study. Neurology 1987;37:717–19.
12. Jelliffe S. The amyotrophic lateral sclerosis syndrome and trauma. J Nerv Ment Dis 1935;82:415–35.
13. Gallagher JP, Sanders M. Trauma and amyotrophic lateral sclerosis: a report of 78 patients. Acta Neurol Scand 1987; 75:145–50.
14. Riggs JE. Antecedent trauma and amyotrophic lateral sclerosis in young adult men. Mil Med 1993;158:55–7.
15. Chancellor AM, Slattery JM, Fraser H, et al. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry 1993;56:1200–6.
16. Cruz DC, Nelson LM, McGuire V, et al. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. Neuroepidemiology 1999;18:101–10.
17. Williams DB, Annegers JF, Kokmen E, et al. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology 1991;41:1554–7.
18. Aggarwal A, Nicholson G. Detection of preclinical motor neurone loss in *SOD1* mutation carriers using motor unit number estimation. J Neurol Neurosurg Psychiatry 2002;73: 199–201.
19. Feeney SJ, McKelvie PA, Austin L, et al. Presymptomatic motor neuron loss and reactive astrocytosis in the *SOD1* mouse model of amyotrophic lateral sclerosis. Muscle Nerve 2001; 24:1510–19.
20. Szczygielski J, Mautes A, Steudel WI, et al. Traumatic brain injury: cause or risk of Alzheimer's disease? A review of experimental studies. J Neural Transm 2005;112:1547–64.
21. Goldman SM, Tanner CM, Oakes D, et al. Head injury and Parkinson's disease risk in twins. Ann Neurol 2006;60: 65–72.
22. Plato CC, Galasko D, Garruto RM, et al. ALS and PDC of Guam: forty-year follow-up. Neurology 2002;58:765–73.
23. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. Neuroepidemiology 2003; 22:217–28.
24. Nelson LM, McGuire V, Longstreth WT Jr, et al. Population-based case-control study of amyotrophic lateral sclerosis in western Washington State. I. Cigarette smoking and alcohol consumption. Am J Epidemiol 2000;151:156–63.
25. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. Neurology 1980;30:453–62.
26. Kondo K, Tsubaki T. Case-control studies of motor neuron disease: association with mechanical injuries. Arch Neurol 1981;38:220–6.
27. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 1986;123:790–9.
28. Granieri E, Carreras M, Tola R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964–1982. Neurology 1988;38:1604–8.
29. Chio A, Meineri P, Tribolo A, et al. Risk factors in motor neuron disease: a case-control study. Neuroepidemiology 1991;10:174–84.