CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 20, NO. 4, 2004, 505–508

0300-7995
doi:10.1185/030079904125003296

COMMENTARY

Soccer, neurotrauma and amyotrophic lateral sclerosis: is there a connection?

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Key words: **Amyotrophic lateral sclerosis – Head injury – Motor neuron disease – Neurodegeneration**

SUMMARY

Trauma has long been hypothesized but never proven to be a risk factor for amyotrophic lateral sclerosis (ALS). This hypothesis may now have a renaissance due to recent reports in the lay press on 'the Italian motoneuron mystery', i.e. the disclosure of 33 diagnosed ALS cases in a subpopulation of 24 000 soccer players of the top three Italian divisions from the 1960s to 1996. Could the repetitive brain trauma that soccer players experience for controlling and advancing the ball with their heads represent an environmental risk factor for developing ALS in genetically predisposed individuals?

By critically reviewing the scarce literature and 'surrounding evidence' (Medline, CDC, lay press, Italian health officials), we have looked for a potential relationship between (1) soccer and head trauma and (2) head trauma and subsequent development of amyotrophic lateral sclerosis. Whereas the brain traumatizing effect of soccer seems to be out of the question, the findings of the few retrospective studies on ALS and neurotrauma are conflicting. Taken together, however, the literature would still support the concept of soccer, head trauma, and ALS being interrelated, with high levels of athleticism/physical activity perhaps playing an additive part. To further clarify this issue, extensive prospective epidemiological investigations on ALS following neurotrauma as well as carefully designed animal studies will have to be conducted.

Introduction: the motoneuron mystery

Newspapers and magazines have been booming recently about an investigation conducted by an Italian judge on what is called *'the motoneuron mystery'* [1]. This ongoing investigation commenced 3 years ago and is evaluating 24 000 soccer players of the top three Italian divisions from the 1960s to 1996. Among them, in a total of 33 individuals the diagnosis amyotrophic lateral sclerosis (ALS) has been made, 13 of them have already died of ALS[2]. Globally, the incidence of ALS in the general population ranges between 0.6 and 2.6 new cases per year per 100 000 inhabitants[3]. Based on comparable diagnostic criteria, the incidence of ALS seems geographically steady, despite differences in terms of genetics, environment and socio-economic level of the areas analysed[3]. In 2003, prevalence of ALS in Northern Italy was 4.1/100 000, mean age at diagnosis 63.8 years, mean survival time after diagnosis 2 years[4]. The prevalence of ALS among the group of Italian football players under investigation is at least 20 times higher than normal. In addition, the onset is unusually early, the soccer players being in their 40s upon diagnosis[5].

The football investigations are among numerous inquiries that this Turin judge has undertaken into drug abuse in Italian sports, including cycling. Although a large number of cancers has been found in cyclists, no cases of motor neuron disease were identified among 6000 Italian cyclists competing over the last 30 years[1]. These data make it unlikely that the strenuous physical exercise or the doping/drug taking habits, common to both soccer players and cyclists, are a *primary* environmental cause of the increased incidence of ALS. Nevertheless, a publication on the final results of the judge's investigation is not yet available.

In the world of sports, soccer is unique because of the purposeful use of the unprotected head for controlling and advancing the ball, a skill obviously placing the player at risk of head injury. This logical conclusion together with reports linking previous head trauma to the risk of developing neurodegenerative disease[6], e.g. Alzheimer (AD), Parkinson, or schizophrenia, has lead us to review the available literature indicating any (in)direct relation between neurotrauma and ALS. From our investigations we postulate that neurotrauma may indeed be a risk factor for ALS, at least in predisposed individuals with genetic mutations of incomplete penetrance.

Literature research methodology

Extensive literature database searches (Medline, Center for Disease Control Traumatic Brain Injury Register) going back to 1967 were performed using the search terms: *ALS and trauma*, *ALS and neurotrauma*, *ALS and soccer/athletes*, *ALS and sports*, *ALS and physical injury*, *ALS and head injury/trauma*. Information on papers older than 1967 was mostly derived from more recent publications.

Searches of the lay press (electronic versions) were based on search terms: *soccer and ALS*, *athletes and ALS*, *trauma and ALS*. This search went back to 1990, with most information derived from recent years (2000–2002). *Telephone contacts* with Italian public health officials were involved in the inquiry on soccer players. This source of information was very restricted due to the confidentiality issues during an ongoing trial.

Is soccer a cause of chronic brain injury?

Head injury in soccer can be the result of contact of the head with another head (or other body parts), ground, goal post, other unknown objects or, in particular, the ball. A plastic-coated leather soccer ball weighs between 396 and 453 g at the start of a match. Older soccer balls became even heavier when soaked with water on muddy fields. A soccer ball can be driven at a speed in excess of 74 miles/h and can deliver enough force to fracture a cheekbone. Force transferred to the forehead at ball contact varies between 500 and 1200 N (Newtons). This force is then quickly dissipated and absorbed by the upper body and torso with a proper heading technique. In comparison, a single punch from a boxer delivers around 6300 N to the head and face; unlike soccer players, the head and brain absorb the majority of this repetitive impact force[7]. Repeated head injury as experienced by boxers can cause *dementia pugilistica*, a distinguished pathological condition characterized by the same molecular markers as AD. Interestingly, boxers with an APO E4 allele develop traumatic encephalopathy of greater severity[8]. Head trauma in turn is a known risk factor for AD in the presence of a predisposing genetic condition[6]. Although Barnett and Curran reported on this in a letter on dementia in retired professional footballers[9], a relationship between soccer and dementia is still a matter of speculation. In a small study, Sortland and Tysvaer found that one third of the players had central cerebral atrophy, probably caused by repeated small head injuries in connection with heading the ball[10]. A coroner court ruled professional soccer player Jeff Astle's death was related to his regularly heading the ball, for which he was famous[11]. Estimates of the number of times a soccer player heads a ball vary from an average of 5–9 per game, with European players heading most frequently[7]. Matser *et al*. uncovered a dose–response relation between headers per season and poor results on cognitive tests. Performance on neuropsychological testing can vary according to the position on the field, with forward and defensive players exhibiting more impairment[12].

Is traumatic brain injury a risk factor for ALS?

Environmental risk factors of neuronegeneration in ALS have been suspected for quite some time. Cycad nuts were found to be a chronic neurotoxic risk for the Guam population; other putative environmental risk factors for ALS include a history of trauma to the brain and spinal cord, strenuous physical activity, exposure to lead, radiation, electrical shocks, welding or soldering materials, employment in paint, petroleum or dairy industries[13]. Etiology/pathogenesis of ALS may reflect a complex interaction between environmental factors and specific susceptibility genes[13].

Table 1. Overview of the available literature associating neurotrauma and ALS

Reference	Country	Number of individuals	Study type	Remarks
Jelliffe SE[18] J Nerv Ment Dis 1935;82:415-35	USA	92 ALS patients	Retrospective	10 head and/or neck trauma
Kondo K and Tsubaki T[19] Arch Neurol 1981;38:220-6	Japan	Study A: 712 patients with motor neuron disease (511 with ALS), 637 controls Study B: 158 ALS patients and 158 matched controls	Retrospective, questionnaire, case control study Retrospective, questionnaire, case control study	Previous head injury in 42 patients with motor neuron disease and in 7 controls, mechanical injury (unspecified location) in 48 ALS patients and 27 controls
Gawel M, *et al.*[20] J Neurol Neurosurg Psych 1983;46:1041-3	UK	63 ALS patients and 61 controls	Retrospective, questionnaire, case control study	Head injury and fractures in 32 patients and 42 controls in the previous 5 years
Gallagher JP, *et al.*[21] Acta Neurol Scand 1987;75:145-50	USA	135 ALS patients and 85 multiple sclerosis controls	Retrospective, questionnaire, case control study	Head/neck trauma in 31 ALS patients and in 13 multiple sclerosis ≥ 1 year before onset of disease
Williams DB, *et al.*[15] Neurology 1991;41:1554-7	USA	821 head injured patients	Retrospective, cohort study	1 ALS case
Strickland D, *et al.*[16] Acta Neurol Scand 1996;94:45-50	USA	25 ALS and 25 other neuro-muscular disease patients	Retrospective, questionnaire, case control study	Severe head, neck, back trauma in 15 ALS patients and in 8 controls
Mandrioli J, *et al.*[4] Neurology 2003;60:683-9	Italy	143 ALS patients	Retrospective, cohort study	9 patients suffered head injury not more than 30 years before disease onset

Can the cumulative concussive effect of soccer heading, in addition to worsening of cognitive functioning, be somehow related to the development of ALS in the presence of a genetic predisposition? An association between ALS and head trauma has never been clearly demonstrated nor has the association between skeletal fracture of head, neck, or spine and pathogenesis of ALS[13,14]. Our survey of the medical literature (Table 1) found only one cohort study of ALS after head injury[15]. In this cohort of 821 individuals who had suffered a head trauma between 1935 and 1974, and were older than 40 years in June 1988, there was one case of ALS, unexpected in a small population of 821. All the other reports retrospectively evaluate the frequency of previous head trauma in small groups of ALS patients, with the severity of head injury being clearly defined in only one of the references[16]. Having a prevalence in the general population of head trauma of approximately 30% in mind, the numbers in the respective papers (see Table 1) appear to represent only severe cases. We, however, propose that mild repetitive head injury rather than severe neurotrauma may be essential for the initiation of slowly advancing neurodegeneration that in turn may increase the risk of ALS, at least in genetically predisposed individuals.

Compared to individuals with other neurological disease, patients with ALS are more likely to have a history of being athletic and slim, according to Scarmeas *et al*. a phenotypic expression of genetic susceptibility to ALS[17]. Hints of such a connection have been floating around for years. Boxer Ezzard Charles, baseball player Catfish Hunter and, of course, baseball icon Lou Gehrig all died of ALS. Three players from the San Francisco 49ers were diagnosed with ALS in the 1980s, and Glenn Montgomery of the Seattle Seahawks lost his life to ALS in 1998[17]. All athletic, all slim. But what would be the respective genes, what would be the genetic penetrance of their mutations? Only some of these genes have been identified[13]. Thus, about 1–2% of the cases of sporadic ALS and 15–20% of familial ALS are caused by mutations of superoxide dismutase 1 (SOD1) which belongs to the endogenous antioxidative system. About 12% of patients with apparently sporadic ALS were found to be heterozygous for a SOD1 mutation. More than 90 SOD1 mutations are known altogether, and all but two (the $SOD1^{D96N}$ and the $SOD1^{D90A}$) provoke dominantly inherited disease. The known action of SOD1 is to convert superoxide to water and hydrogen peroxide. The fact that transgenic expression of a human SOD1 mutation (SOD^{G93A}) leads to an ALS-like disease in mice underlines the pathophysiological significance of this mutation[13]. Apart from a single major gene responsible for the disease, ALS may also be caused by certain genetic constellations explaining the so-called sporadic cases that require co-factors to occur. Among these co-factors, neurotrauma is likely to play a

prominent role. Athleticism or strenuous physical exercise are also apparently implicated. A common denominator of some of these co-factors might be the chronic exhaustion of the body's antioxidative capacity.

Conclusions: where to go from here?

Although neurotrauma appears to be a risk factor for ALS, at least in genetically predisposed individuals, only a prospective evaluation of a large cohort of neurotrauma victims can definitely provide an unbiased answer to this controversy. In addition to epidemiological approaches, experimental studies are essential, investigating long-term consequences of traumatic brain injury and revealing mechanisms underlying neurotrauma-induced neurodegeneration, perhaps also in SOD1 transgenic (ALS) mice.

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Paper CMRO-2487, *Accepted for publication*: 12 December 2003
Published Online: 12 February 2004
doi:10.1185/030079904125003296