Arq Neuropsiquiatr 2007;65(2-A):189-195

A CLINICAL EPIDEMIOLOGICAL STUDY OF 251 CASES OF AMYOTROPHIC LATERAL SCLEROSIS IN THE SOUTH OF BRAZIL

Lineu Cesar Werneck, Ruth Bezerra, Octavio da Silveira Neto, Rosana Herminia Scola

ABSTRACT - *Objective:* To study the clinical forms of amyotrophic lateral sclerosis (ALS) and the possible presence of risk factors in order to verify if there is any difference between cases in Paraná, Brazil. *Method:* We studied 251 cases, all of which fulfilled the diagnosis criteria proposed in El Escorial (WFN). Between 1977 and 2004, 157 male and 94 female patients were examined. *Results:* 220 cases were classified as ALS-Spinal Onset (ALS-SO), 24 as ALS-Bulbar Onset (ALS-BO) and 7 as Familial ALS. The mean age at time of evaluation was 54.4±12.3 years, and symptoms had started 17.9±15.7months previously. In the group studied, statistical relationships were found between heavy occupations and males; previous surgeries and females; ALS-BO and dysphagia and dysarthria in females; and ALS-SO and males, cramps, weakness, muscle atrophy, hypertonia, increased deep tendon reflex and abnormal gait. *Conclusion:* The average age at time of evaluation was lower than that registered in the literature but similar to the Brazilian series. Domestic work and heavy occupations appear to be related to precocious perception of the symptoms by interference with daily functions. The socioeconomically higher classes seek medical care early. There was no relationship with exposure to toxic agents or trauma.

KEY WORDS: amyotrophic lateral sclerosis, motor neuron disorders.

Estudo clínico epidemiológico de 251 casos de esclerose lateral amiotrófica no sul do Brasil

RESUMO - *Objetivo:* Estudar as formas clínicas de esclerose lateral amiotrófica (ELA) e possíveis fatores de risco, a fim de verificar se existem diferenças entre os casos do Paraná, Brasil. *Método:* Estudamos 251 casos entre 1977 e 2004, que preencheram os critérios propostos em *El Escorial* (WFN), sendo 157 do sexo masculino e 94 do feminino. *Resultados:* Foram classificados como ELA de início espinhal (ELA-IE) 220 casos, ELA de início bulbar (ELA-IB) 24 casos e 7 casos como ELA familiar. A idade média na avaliação foi 54,4±12,3 anos cujos sintomas iniciaram 17,9 ±15,7 meses antes. Foram encontradas relações estatísticas entre ocupação que demandam esforços físicos com homens; ciru rgias prévias com mulheres; ELA-IB, disfagia e disartria, mulheres; ELA-IE, homens, câimbras, fraqueza, atrofia muscular, hipertonia, aumento de reflexos profundos e marcha anormal. *Conclusão:* A idade média na época da avaliação foi menor que a registrada na literatura, mas similar às séries brasileiras. Trabalhos domésticos e ocupações que demandam esforços físicos estão relacionados com a percepção precoce dos sintomas pelas inferências com as funções diárias. As classes sócio-econômicas melhores situadas procuram atendimento médico mais cedo. Não foram encontradas relações com a exposição a agentes tóxicos e traumatismos.

PALAVRAS-CHAVE: esclerose lateral amiotrófica, doenças do neurônio motor inferior.

Amyotrophic lateral sclerosis (ALS) is a degenerative disease involving the upper and lower motor neurons and is distributed throughout the world. Incidence of the disease varies from 0.6 to 2.6 cases per 100,000 inhabitants/year. Clinical presentation of ALS is not uniform and varies according to the population studied[1-8].

The etiology of ALS is not well known, and several hypotheses have been proposed in an effort to find a relationship with a number of exogenous risk factors, such as physical activity, traumatisms, surgery and exposure to toxic substances [3,7,9-15]. The description of family cases associated with mutations in the genetic codes of superoxide dismutase enzymes, the search for genetic markers and the possibility of their expression led to a search for exogenous factors as triggering mechanisms in cases of sporadic ALS[16].

Our center is a public hospital attending a large number of manual workers and farmhands exposed to agricultural pesticides and also used to heavy work.

Neurology and Neuromuscular Service, Internal Medicine Department, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba PR, Brazil. This research was supported in part by CAPES and CNPq.

Received 18 July 2006, received in final form 14 November 2006. Accepted 2 December 2006.

Dr. Lineu Cesar Werneck - Rua Gal. Carneiro 181 / 3° andar - 80060-150 Curitiba PR - Brasil. E-mail: werneck@ufpr.br

This population is ideal for testing the above hypothesis, as it can be compared with a private clinic population living in a larger city, enjoying better socioeconomic conditions and with predominantly sedentary occupations. In this study we investigate initial symptoms, possible risk factors and neurological findings in patients with bulbar and spinal-onset, as well as familial, ALS.

METHOD

We selected all the cases catalogued as motor neuron disorders attended between 1977 and 2004 in the Neurology and Neuromuscular Disorders Service of the Internal Medicine Department at the Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (HC) and patients evaluated in the Private Clinic (PC) of one of the authors (LCW). We only selected patients from the PC who had complete clinical records, thus allowing a diagnosis and complete evaluation to be made. All the information reported below was obtained in the first evaluation. The records had to have information about detailed clinical history and complete physical and neurological examinations, as well as reports of previous diseases (trauma, surgery, intoxications) and family information.

We examined the records for information regarding age at the time of evaluation, age at onset of the first symptoms recalled by the patient, race, family history, origin of the cases (HC or PC), occupation, previous diseases, previous surgical procedures and severe traumatisms. Cases were classified in terms of occupation and grouped according the IBGE (Brazilian Institute of Geography and Statistics) 2000 census. The following classifications were used for the types of activity performed: 1) senior members of public authorities, heads of public-interest organizations and companies and managers; 2) professionals in the sciences and arts (university level); 3) secondary-level technicians; administrative workers; store and market salespersons; 4) agricultural, forestry and fishery workers and hunters; 5) workers involved in the production of industrial goods and services; 6) maintenance and repair workers; 7) members of the armed forces; 8) housewives (women).

Cases were also classified according to initial symptoms: the presence of fasciculation, dysphagia, dysphonia, dysarthria, cramps, muscle pains, weight loss, urinary incontinence and muscular weakness. In the neurological examination, emphasis was given to fasciculation, atrophy and muscle tonus, muscular strength in the upper limbs (UL) and lower limbs (LL) classified according to the Medical Research Council (MRC) Scale, deep tendon reflexes in UL and LL, superficial reflexes and gait.

The following results of laboratory tests were reported: creatine kinase, lactic dehydrogenase, and aminotransferase activity; complete blood count; sedimentation rate; glucose, creatinine, calcium, magnesium, sodium and potassium levels; protein electrophoresis; and cerebral spinal fluid tests (glucose, cytology, proteins and electrophoresis).

All cases had to have an electromyography examination compatible with lower motor neuron disorder, namely fibrillations, positive sharp waves, fasciculation (either associated or not with a reduction in recruitment), increase in duration and amplitude of motor unit potentials (MUPs) with an excess of large and long polyphasic potentials depending on the time at which the examination was performed) in at least two body segments. Sensitive nerve conduction velocities had to be normal. Motor nerve conduction velocities had to be normal in the initial phase, with a slight reduction afterwards suggesting axonal degeneration being accepted in the absence of conduction block, which was sought in the four limbs[17-19].

For the diagnosis, the criteria proposed in *El Escorial* and accepted by the World Federation of Neurology were used. According to these criteria, the patient must have signs of upper motor and lower motor neuron involvement, with evidence of dissemination in other parts of the body, such as the brain stem and cervical, thoracic and lumbar spinal cord. Other diseases must also be excluded for the diagnosis, and this can sometimes be done by electromyography or radiological studies[20,21]. Only those cases with enough information in the records that fulfilled the *El Escorial* criteria were included, as some cases had been seen before these criteria were published.

Cases were classified as: 1) Sporadic-Classical Amyotrophic Lateral Sclerosis Spinal Onset (ALS-SO) when the patients started with motor symptoms below the foramen magnum, and Amyotrophic Lateral Sclerosis Bulbar Onset (ALS-BO) when the symptoms began with clinical involvement of the motor cranial nerves; and 2) Familial Amyotrophic Lateral Sclerosis (ALS-F). Cases were classified according to symptoms and signs in the initial clinical evaluation as follows: 1) Defined: signs of upper motor neuron disorder (UMN) and lower motor neuron disorder (LMN) in three regions, such as the brain stem, and cervical, lumbar and sacral regions; 2) Probable: signs of UMN and LMN disorders in two different regions, with LMN signs rostral to UMN; 3) Possible: signs of UMN and LMN disorder in one region or LMN disorder in two or three regions; 4) Suspect: evidence of involvement of LMN in two or more different regions. In addition to the signs of UMN or LMN, for this classification all cases had to have an electromyography result compatible with lower motor neuron involvement according to the criteria listed above.

The data were analyzed using descriptive statistics, frequency, chi-square tests with Yates correction and the Fischer test.

RESULTS

Initially, 283 cases were selected. Of these, 32 were excluded for the following reasons: 5 because routine protein electrophoresis showed that they had a gammopathy, 3 because they had urinary incontinence and precocious dementia, 1 because the patient was diagnosed as having juvenile spinal muscular atrophy (Kugelberger-Wellander Disease) during evolution and follow-up, 11 because they only had lower motor neuron involvement (progressive muscle atrophy), 6 because of bulbar spinal atrophy

Table 1. Classification of 226 cases of motor neuron disorders.

	Males (%)	Females (%)	Total (%)
Sporadic			
ALS spinal onset	144 (57.4)*	76 (30.2)	220 (87.6)
ALS bulbar onset	9 (3.6)	15 (6.0)*	24 (9.6)
Familial			
Familial ALS	4 (1.6)	3 (1.2)	7 (2.8)
Total	157 (62.6)	94 (37.4)	251

ALS, amyotrophic lateral sclerosis; *p<0.05 (Chi square p=0.011 for spinal onset in males and p=0.008 for ALS bulbar onset in females).

(Kennedy disease), 3 because of motor neuron disorder and dementia, 1 because of possible primary lateral sclerosis, and 2 because the patient had not been submitted to electromyography despite all the signs and indications suggestive of ALS. The remaining 251 cases were classified as amyotrophic lateral sclerosis.

Using the proposed criteria, ALS-SO predominated among the 251 cases, followed by ALS-BO and ALS-F. The ALS-BO was predominant in the females (Table 1).

In terms of the clinical signs, the "possible" classification predominated, with 86 cases (34.3%), followed by "probable" with 68 (27.1%), "defined" with 60 (23.9%) and "suspect" with 37 (14.7%). These classifications change over time because of disease progression. When followed up subsequently, the "suspected", "probable" and "suspect" cases presented signs of UMN and LMN involving three segments, thus allowing the diagnosis to be confirmed. The long term follow-up was not the scope of this paper.

The average age at the time of evaluation was 54.4±12.3 years. The mean time since the onset of symptoms was 17.9±15.7 months, with no statistical difference between males and females. The proportion of Caucasian patients was 95.2%. In terms of origin, 139 (55.4%) of the cases were from the HC and the remainder from the PC. There was a statistical difference between the time of onset of the symptoms and the origin of the patients. The HC cases sought medical assistance on average 20.71±18.22 months after onset of the symptoms, and those from the private clinic sought assistance 14.55±11.22 months after onset (p=0.004) (Mann-Whitney).

With regard to occupation, the following categories predominated: women carrying out household tasks (housewives); agricultural, forestry and fishery workers and hunters; and workers involved in the production of industrial goods and services. Compared with the expected figure for the population of the South of Brazil (the States of Paraná, Santa Catarina and Rio Grande do Sul) in the 2000 census (10,483,482 people with declared employment and 6,171,202 women without a defined occupation, whom we assumed were working as housewives). We observed that there was a larger incidence than was expected among administrative workers, agricultural workers, professionals with a third-level qualification and maintenance and repair workers. On the other hand, we found a lower incidence than was expected for heads of public authorities and managers, secondary-level technicians, shop workers and women performing household chores. Because of the small number of cases compared with the population of the South of Brazil, statistical correlations based on our findings could lead to misleading results. We therefore did not pursue this issue further (Table 2).

Eighty-nine cases, of whom 58 were male, were involved in sedentary occupations (business manager, attorney, administrative clerk, bank clerk, dealer, bookkeeper, dentist, engineer, pharmacist, government employee, priest, teacher and military personnel); 56, all of whom were female, were involved in domestic activities (housewife, dressmaker, charwoman); 106 cases, of whom 7 were women, were involved in heavy activities (carpenter, electrician, coil maker, mechanic, metalworker, driver, baker, mason, farm worker, gas-station attendant and shoemaker). In the latter group, there was a statistically significant difference between sex and occupation in terms of heavy work and domestic activities, as males are involved in heavy occupations and at-risk occupations, while females usually work at home, where they perform "lighter work" (Chi-square p=0.000). No statistical difference was found between sedentary work and gender (p=0.6180).

We found 70 cases of patients who reported previous illnesses (42 men and 28 women), with 20 hav-

Table 2. Occupation frequencies (Observed vs Expected) in 251 patients with amyotrophic lateral sclerosis.

Type of job	Number of cases	Observed %	Expected %*	Observed/ Expected
Sedentary				
Senior members of public authorities, heads of public interest organizations and companies and managers;	2	0.80	2.98	0.27
Professionals in the sciences and arts (university level)	16	6.37	3.73	1.71
Secondary-level technicians	5	1.99	4.77	0.42
Administrative workers	26	10.36	5.05	2.05
Store and market salespersons	20	7.97	16.30	0.49
Members of the armed forces, police officers and firefighters	2	0.70	0.52	1.34
Heavy				
Agricultural, forestry and fishery workers and hunters	58	23.11	12.23	1.89
Workers involved in the production of industrial goods and services	56	22.31	16.21	1.38
Repair and maintenance workers	6	2.39	1.52	1.57
Domestic activities				
Housewives (women)	60	23.90	35.95	0.66
No defined occupation	0	0.00	0.73	0.00

*IBGE data, Demographic census, 2000 (10,996,193 people with a defined occupation plus 6,171,202 women without a declared occupation and classified as housewives in the South of Brazil (the States of Paraná, Santa Catarina and Rio Grande do Sul).

Table 3. Relationship between symptoms at time of evaluation and gender in 251 cases of amytrophic lateral sclerosis.

Symptoms	Males Nº cases	Females Nº cases	Total
Generalized weakness	151	89	240
Fasciculation	96	49	145
Cramps	65	29	94
Dysphagia	42	46	88**
Dysarthria	38	34	72*
Weight loss	45	25	70
Dysphonia	30	23	53
Muscle pain	30	16	46
Tremors	8	5	13
Urinary urgency	2	1	3

*=0.042; **p=0.001 (Chi-square).

Table 4. Statistical relationship <0.05 (Chi-square) by type of amyotrophic lateral sclerosis.

	ALS-SO	ALS-BO	ALS-F
Nº cases	220	24	7
Gender	144 p=0.011 (males)	15 p=0.008 (females)	NS
Family history			p= 0.000
Dysphagia	68	19 p=0.000	
Dysphonia	34	18 p=0.000	
Dysarthria	53	19 p=0.000	
Cramps	87 p=0.029	5	
Weakness	215 p=0.001	19	
Muscle atrophy	185 p=0.016	14	
Hypertonia	109 p=0.022	7	
Increased deep Tendon reflexes lower limbs	142 p=0.015	12	
Abnormal gait	148 p=0.000	3	

ALS-SO, amyotrophic lateral sclerosis spinal onset; ALS-BO, amyotrophic lateral sclerosis bulbar onset; ALS-F, familial amytrophic lateral sclerosis.

ing a history of severe traumatisms (15 men and 5 women) and 15 having had exposure to toxic substances (11 men and 4 women). However, there was no statistically significant diff e rence between sexes. In this group, 48 cases, of whom 24 were men and 24 women, had had previous surgeries, and this was found to be statistically significant (chi-square p=0.046).

In the first evaluation, the most frequent complaint was muscular weakness, followed by fasciculation and cramps. Less common were dysphagia, dysarthria, weight loss, dysphonia and muscular pain. Tremors and urinary urgency were rare. In this group of patients, a statistical difference was found for dysphagia and dysarthria, with predominance in the females, but not for dysphonia (Table 3).

In the examination, hyperactive deep tendon reflexes predominated to the same extent in both the upper and lower limbs (65.7%) and were absent in 4% of the cases. Babinski's sign was present in 32.6% of the cases, and cutaneous abdominal reflex was absent in just 4 cases. Hypertonia was found with spasticity in 46.6% of the cases, hypotonia in 15.9% and normal muscle tonus in 37.5%. No statistical significance was found in terms of gender and muscle tonus or gender and deep and superficial reflexes.

In general, muscular strength was normal, with a slight reduction in half the cases at the time of the evaluation. A few patients, however, arrived for examination with significant difficulties. There was no significant difference between the decrease in strength in UL and in LL.

In the first examination, generalized fasciculation was found in 55.3% of the cases and localized fasciculation in 29.5%. Fasciculation was absent in 15.1% of the cases. Muscular atrophy was localized in 67.3% of the cases and involved one or two segments on the same side or on opposite sides. Tongue atrophy as well as neck atrophy was rare in the evaluation, representing less than 1.0% of all the cases. In 20.7% of the cases, no muscle atrophy was found. Gait showed alterations in 61.7% of the cases, and was normal in 39.4%. There was no statistical difference between the genders in terms of fasciculation, muscle atrophy and gait.

Each of the variables was examined in terms of the type of ALS presentation and the clinical findings in the evaluation to check whether there was any statistical variation with probability lower than 0.05. We identified a significant relationship between ALS-SO and males, cramps, weakness, muscle atrophy, hypertonia, increased deep tendon reflexes and abnormal gait. There was a positive relationship between ALS-BO and gender (females), as well as dysphonia, dysarthria and dysphagia. Family history was related to ALS-F, which was to be expected, considering the type of randomization performed. The other variables had no relationship with the type of presentation, thus showing that the other signs and symptoms are common to all types (Table 4).

With regard to the origin of the patients, we found more Afro-Brazilian patients and patients involved in heavy occupations in the HC population, while sedentary occupations predominated in the PC population. There were more surgeries in the PC, where more fasciculation and cramps were also reported. More generalized fasciculation was found in the private clinic, but a greater number of cases of localized fasciculation were noted in the HC during examination. At first evaluation, abnormalities of gait were found in greater numbers among HC patients. These differences can be explained by social, economic and cultural factors, because part of the financially less well-off population cannot afford to go to a private clinic so frequently and only seek medical care later. In addition, they pay no attention to the symptoms in the beginning, because these do not interfere with their normal daily activities. The greater number of surgeries in the PC reflects the better medical care that the financially better-off can afford.

DISCUSSION

The incidence of the different types of motor neuron disease (MND) varies according to the time and place being studied, i.e. the place where patients are evaluated. Classic ALS shows an incidence between 51.3% and 91%[2,4,5,8,22-26]. Our study is a retrospective one and was based on reviews of records, bearing in mind that the "El Escorial" criteria only started being used after 1994 and that only those cases with all the required information were included[20]. We did not find a reason for the statistically significant incidence of the ALS-BO form in females, which agrees with the findings of Dietrich Neto and col.[26]. We found a lower incidence of familial ALS than was found in the literature, in which an incidence of between 5 and 10% related to mutations of a gene located in chromosome 21q22.1 is reported. This gene codifies the Cu^{2+} and Zn^{2+} superoxide dismutase (SODI1) enzymes involved in the elimination of free radicals. More than 70 mutations were identified in this gene[16]. This low incidence may be due to the extensive population migration that occurs in Brazil and to the lack of communication between family members, who are unaware of the state of their relatives' health.

The clinical form that predominated in this study was the "probable" one, with the lowest incidence being "suspect" forms. As has already been pointed out in the literature, classification by clinical form raises a number of problems, as it depends on when the patients are examined. If the patients are examined late in the course of the disease, most of them will be in the defined form, thus reducing the number of "possible" and "suspect" ones[25,27].

The average age at the time of evaluation was similar to some published series[4,11,26,28,29], lower than others[1,2,5,6,8,24,30-32] and higher than others[25,33]. However,

the duration of the symptoms when the diagnosis was made was longer than that in some reported series[8,9,29,30] and shorter than others[2,32]. This period was shorter in the patients from the private clinic, probably because they enjoyed better socioeconomic conditions.

The predominance of the male gender is already a well-known fact in the literature, and was also found in our casuistics[4,22,24,29]. In the analysis of the activities and occupations in terms of gender, we observed that the majority of men are active in occupations that are considered to be heavy, while most of the women are involved in domestic activities. This again raises the hypothesis that physical activities requiring the use of strength have some relationship with the triggering of the disease[7,9,13,15,34-37]. However, other studies did not find any relationship[11,14,29,38,39]. There may possibly be other factors that act together in the triggering of the disease besides heavy work. On the other hand, to say that domestic work is light work does not stand up to analysis either, as some of the female patients work longer hours at home than men do at their own jobs, a situation which is quite common in Brazil.

When the symptoms are analyzed in relation to the types of ALS, we can see that the number of females is statistically more significant in the cases of ALS-BO, as are the symptoms of dysphonia, dysarthria and dysphagia. This fact has already been observed, mainly in older women, but there is no plausible explanation[2,11,25]. However, it has been suggested that in women the glossolaryngeal muscles are more vulnerable in neurodegenerative diseases than the glossopharyngeal ones[27].

Traumatism has been pointed out in several papers as a possible factor in the triggering of ALS[7,12,40]. However, other studies have not found any association[9,11,29,41]. This discrepancy may be due to the excessive importance attached to the symptoms by patients, who try to establish a relationship between the disease and some other factor. Neither should we forget that patients occasionally suffer a trauma due to the reduction of muscle strength at an initial stage of the disease as a result of functional muscle deficit just before the diagnosis is made. The greater number of surgeries in women calls for a study with control cases before this fact is considered relevant. The greater number of surgeries in the economically better-off group is a reflection of the easier access this group has to medical care.

Babinski's sign and the changes in gait resulting from spasticity had a statistical relationship with ALS cases, suggesting that the upper motor neurons are involved at the same time as the lower motor neurons.

In summary, ALS-SO cases predominated in our series, and the most frequent clinical form at first evaluation was the "probable" one. Average age at time of evaluation was 54.4 years, and patients in better socioeconomic circumstances were diagnosed, on average, 6 months earlier than those in worse socioeconomic circumstances. Cases in males predominated, and there was a predominance among women involved in sedentary and domestic occupations and among men involved in heavy occupations. There was a greater number of previous surgeries in females. The major symptoms were fasciculation, with a greater number of bulbar symptoms in women. Changes in gait and signs of long tract dysfunction in cases of ALS-SO predominated without any relationship to gender. Muscle involvement was practically identical in UL and LL.

Acknowledgements – We thank to Mr. Colin Bowles for manuscript review.

REFERENCES

1. Lopes-Vega KM, Calleja J, Combarros O, Pólo JM, Berciano J. Motor neuron disease in Cantabria. Acta Neurol Scand 1988;77:1-5.
2. Tysnes O-B, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland County, Western Norway. Acta Neurol Scand 1991;83:280-285.
3. Chancellor AM, Warlow PC. Adult onset motor neuron disease: worldwide mortality, incidence and distribution since 1950. J Neurol Neurosurg Psichiatry 1992;55:1106-1115.
4. Giagheddu M, Macia V, Cannas A, et al. Amyotrophic lateral sclerosis in Sardinia, Italy: an epidemiologic study. Acta Neurol Scand 1993;87: 446-454.
5. Bettoni L, Bazzani M, Bortone E, Dascola I, Pisani E, Mancia D. Steadiness of amyotrophic lateral sclerosis in the province of Parma, Italy, 1960-1990. Acta Neurol Scand 1994;90:276-280.
6. McGuire V, Longstreth WT Jr, Koepsell Y, van Belle G. Incidence of amyotrophic lateral sclerosis in three counties in western Washington State. Neurology 1996;47:571-573.
7. Rossati G, Pinna L, Granieri E et al. Studies on epidemiological, clinical and etiological aspects of ALS disease in Sardinia, Southern Italy. Acta Neurol Scand 1977;55:231-244.
8. Argyriou AA, Polychronopoulos P, Papapetropoulos S, et al. Clinical and epidemiological features of motor neuron disease in south-western Greece. Acta Neurol Scand 2005;111:108-113.
9. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. Neurology 1980; 30:453-462.
10. Riggs JE. Trauma and amyotrophic lateral sclerosis [letter]. Arch Neurol 1985;42:205.
11. Li T-M, Alberman E, Swash M. Clinical features and associations of 560 cases of motor neuron disease. J Neurol Neurosurg Psichiatry 1990; 53:1043-1045.
12. Armon C, Kurland LT, Smith GE, Steele JC. Sporadic and western pacific amyotrophic lateral sclerosis. In Smith RA (Ed). Handbook of amyotrophic lateral sclerosis. New York: Marcel Dekker, 1992:93-131.
13. Steiner I, Birmanns B, Panet A. Sun exposure and amyotrophic lateral sclerosis [letter]. Ann Intern Med 1994;120:893.
14. Longstreth Jr WT, McGuire V, Koepsell TD, Wang Y, van Belle G. Risk of amyotrophic lateral sclerosis and history of physical activity. A population-based case-control study. Arch Neurol 1998;55:201-206.

15. Chio A, Benzi G. Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian occupational football players. Brain 2005;128:472-476.
16. Robberecht W. Genetic markers of ALS. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1(Suppl 2):S57-S59.
17. Dumitru D. Electrodiagnostic medicine. Philadelphia: Hanley & Belfus, 1995
18. Cornblath DR, Kuncl EW, Mellits ED, et al. Nerve conduction studies in amyotrophic lateral sclerosis. Muscle Nerve 1992;15:1111-1115.
19. Behni M, Kelly JJ. Role of electromyography in amyotrophic lateral sclerosis. Muscle Nerve 1991;14:1236-1241.
20. 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):S96-S107.
21. Mitsumoto H. Diagnosis and progression of ALS. Neurology 1997;48 (Suppl 4):S2-S8.
22. Lima JMB, Mesquita N, Duro LAA, Furtado AB. Epidemiological; aspects of ALS in Rio de Janeiro City. Rev Bras Neurol 1983;19:75-78.
23. Leone M, Chandra V, Shoenberg BS. Motor neuron disease in the United States, 1971 and 1973-1978: patterns of mortality and associated conditions at the time of death. Neurology 1987;37:1339-1343.
24. Scarpa M, Colombo A, Panzetti P, Sorgato P. Epidemiology of amyotrophic lateral sclerosis in the province of Modena, Italy. Influence of environmental exposure to lead. Acta Neurol Scand 1988;77:456-460.
25. Castro-Costa CM, Oriá RB, Machado-Filho JA, et al. Amyotrophic lateral sclerosis: clinical analysis of 78 cases from Fortaleza (Northeastern Brazil). Arq Neuropsiquiatr 1999;57:761-774.
26. Dietrich-Neto F, Callegaro D, Dias-Tosta E, Silva HA, Ferraz ME, Lima JMB, Oliveira ASB. Amyotrophic lateral sclerosis in Brazil. 1988 national survey. Arq Neuropsiquiatr 2000;58:607-615.
27. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman OM. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria. Arch Neurol 2000;57:1171-1176.
28. Gubbay SS, Kahanae E, Zilbier W, Cooper G, Fintov G, Leixosite Y. Amyotrophic lateral sclerosis: a study of its presentation and prognosis. J Neurol 1985;232:295-300.
29. Juergens MS, Kurland LT, Okazaki H, Mulder DW. ALS in Rochester, Minnesota, 1925-1977. Neurology 1980;30:463-470.
30. Christensen PB, Pedersen EH, Jensen NB. Survival of patients with amyotrophic lateral sclerosis in 2 Danish counties. Neurology 1990;40: 600-604.
31. Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. Neurology 2002;59:280-282.
32. Hudson AJ, Davenport A, Hader WJ. The incidence of amyotrophic lateral sclerosis in southwestern Ontario, Canada. Neurology 1986;36: 1524-1528.
33. Damiani IT, Tilbery PC. Esclerose lateral amiotrófica. Estudo clínico. Arq Méd Hosp Fac Clin Méd Santa Casa (São Paulo) 1987;7:43-49.
34. Bharucha NE, Schoenberg BS, Raven RH, Pickle LW, Byar DP, Mason TJ. Geographic distribution of motor neuron disease and correlation with possible etiologic factors. Neurology 1983;33:911-915.
35. Jokelainen M. Amyotrophic lateral sclerosis in Finland. I. An epidemiologic study. Acta Neurol Scand 1977;56:185-193.
36. Holloway SM, Emery AEH. The epidemiology of motor neuron disease in Scotland. Muscle Nerve 1982;5:131-133.
37. Scarmeas N, Shid T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. Neurology 2002;59:773-775.
38. Liebetanz D, Hagemann K, von Lewinski F, Kahler E, Paulus W. Extensive exercise is not harmful in amyotrophic lateral sclerosis. Eur J Neurosci 2004;20:3115-3120.
39. Valenti M, Pontieri FE, Conti F, Altobelli E, Mazoni T, Frati L. Amyotrophic lateral sclerosis and sports: a case-control study. Eur J Neurol 2005;12:223-225.
40. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 1986;123:790-799.
41. Grensham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and history of skeletal fracture: a case-control study. Neurology 1987;37:717-719.