

AMYOTROPHIC LATERAL SCLEROSIS IN BRAZIL 1998 NATIONAL SURVEY

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ABSTRACT - Objectives: To assess the epidemiologic characteristics of amyotrophic lateral sclerosis (ALS) in Brazil in 1998. **Method:** Structured Clinical Report Forms (CRFs) sent to 2,505 Brazilian neurologists from January to September 1998 to be filled with demographic and clinical data regarding any ALS patient seen at any time during that year. **Results:** Five hundred and forty CRFs were returned by 168 neurologists. Data on 443 patients meeting the criteria of probable or definite ALS according to El Escorial definition were analysed: 63 probable (14.2%) and 380 definite (85.8%). Two hundred and fifty-nine (58.5%) of the patients were male, mean age of onset was 52. Spinal onset occurred in 306 patients (69%); bulbar onset in 82 (18.5%), and both in 52 (11.7%). Twenty-six (5.9%) had a family history of ALS. Two hundred and fifty-nine (58.6%) were seen by private practitioners, and 178 (40.2%) at a hospital clinic. Age-adjusted incidence shows a peak incidence at the 65-74 years old range. **Conclusions:** The disease's characteristics are similar to those described in international studies, except for age of onset (Brazilian patients are younger). This difference is not confirmed when figures are age-adjusted.

KEY WORDS: amyotrophic lateral sclerosis, ALS, epidemiology, prevalence, incidence.

Esclerose lateral amiotrófica no Brasil: registro nacional, 1998

RESUMO - Objetivos: Avaliar as características epidemiológicas da esclerose lateral amiotrófica (ELA) no Brasil durante o ano de 1998. **Método:** Formulários estruturados enviados a 2.505 neurologistas brasileiros de janeiro a setembro de 1998 para serem preenchidos com dados demográficos e clínicos de todos os pacientes com ELA atendidos no ano de 1998. **Resultados:** Quinhentos e quarenta formulários retornaram, enviados por 168 neurologistas. Dados sobre 443 pacientes que se enquadravam nos critérios de ELA provável ou definida de acordo com El Escorial foram analisados: 63 provável (14,2%) e 380 definida (85,8%). Duzentos e cinquenta (58,5%) eram do sexo masculino. A idade média de aparecimento dos primeiros sintomas foi de 52 anos. O início em membros ocorreu em 306 pacientes (69%), bulbar em 82 (18,5%) e generalizada em 52 (11,7%). Vinte e seis (5,9%) tinham história familiar. Duzentos e cinquenta e nove (58,6%) foram atendidos em clínicas ou consultórios, e 178 (40,2%) em ambulatório de hospital. Ajustando para a distribuição da população brasileira segundo faixa etária, a maior incidência ocorre entre 65 e 74 anos de idade. **Conclusões:** As características epidemiológicas da doença são semelhantes àquelas descritas em estudos internacionais, exceto para idade dos primeiros sintomas (pacientes brasileiros são mais jovens). Esta diferença desaparece quando os valores são ajustados para idade.

PALAVRAS-CHAVE: esclerose lateral amiotrófica, ELA, epidemiologia, prevalência, incidência.

Amyotrophic lateral sclerosis (ALS) is an invariably fatal neurodegenerative disease encompassed in the spectrum of neuromuscular disorders (NMD) and characterized by progressive

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loss of upper and lower motor neurones, leading to muscle weakness and death. Usually 50% of the patients die within 3-4 years of symptoms onset¹. The only available drug treatment, riluzole, prolongs life but has not been shown to prevent the disease's fatal outcome². ALS's incidence and prevalence rates vary widely from one country to another. The prevalence may range from 0.8/100,000 population in Mexico, to 8.4/100,000 in UK³. This variation can be related to underdiagnosis, but race as well as latitude have been held at least partially responsible for such differences⁴. In Brazil, there is little epidemiologic data available. Due to the disease's short course and fatal outcome, the mortality rate could be an indirect measure of the incidence rate⁵, but more than 15% of the death certificates in Brazil state "unknown causes" as underlying cause of death, making national results unreliable as a whole⁶, except for some rare regional surveys.

Three Brazilian incidence studies, based on adjudicated death certificates are worth mentioning. In the study by Lima et al. death certificates from the city of Rio de Janeiro, covering 10 years (1965-74), were analysed. ALS's annual mortality rate ranged from 0.3 to 0.9/100,000 population⁷. The highest rates were observed in the years 1971 through 73. In Gomes' survey, 1979 through 1986, the annual mortality rate ranged from 0.35 to 0.55/100,000 in Rio de Janeiro city⁸. In 1998, an updated survey by Moraes found ALS mortality to vary from 0.2 to 0.32/100,000 in 91-94, in the city of São Paulo, and 0.36-0.41/100,000 during the years 1995 through 97 (Table 1)⁹.

To date, in Brazil, no attempt has been made to put together a comprehensive database to assess ALS's other epidemiologic aspects, such as sex distribution, time from onset to diagnosis and tests performed. Such studies are confined to referral centers. In 1983, a study from Rio de Janeiro, analysing data on 136 patients showed 68% were male, 75% had limb onset, 80% presented their first symptoms before 60 years old⁷. In 1998, a study from São Paulo on 51 patients from yet another referral center found a male to female ratio of 1.7, limb onset in 78%, familial ALS in 4%.¹⁰ In 1999, a retrospective study performed on 78 patients from Ceará (a northeastern state) found 21% of them to be of juvenile (15-29 years old) sporadic form. Ninety-one percent had spinal onset, and male-female ratio was 1.8/1¹¹.

Brazil's dimensions (>8 million km², 160 million inhabitants, 4,500 neurologists), inequities regarding access to health services, and the lack of a patient association, as of 1998, were other factors to hinder the epidemiologic knowledge of the disease. The present study was designed to bridge this gap, assessing the disease's characteristics in a comprehensive survey. The primary objective was to assess demographic and disease data from as many ALS patients as possible, seen in 1998, irrespective of the date of diagnosis, and diagnosed with probable or definite ALS according to the World Federation of Neurology (WFN) criteria¹². Our patient population should be as comprehensive as possible, coming from referral centers as well as private clinics, in order to compare it to other countries' data, and to avoid the bias described by Lee et al. in 1995: when comparing the outcome of ALS patients from the general population to that of a referral center, the authors found that the 5-year survival rate was 4% for the cohort as compared to 21% for the referral center population, due to factors independent of treatment¹³.

METHOD

From January to September 1998, invitation letters and forms were sent to 2,505 neurologists found through HMO booklets, congress lists and the Brazilian Neurological Association, describing the study's objectives and asking them to fill a one-page long clinical research form (CRF) per patient under his/her care in 1998. Each neurologist received initially 2 blank forms to be filled with his patients' data. Mail charges were pre-paid.

Data were collected on demography (sex, date and place of birth, place of consultation) and disease characteristics (date of symptoms' onset; date of diagnosis; date of death; classification according to El Escorial criteria; family history; site of onset; tests performed).

Interim analyses were performed every 3 months, and reports were sent to all participating (responding) doctors.

A control of the number of CRFs sent and received from each physician, and an immediate trigger of more blank CRFs prevented them from running out of forms, and more forms could be sent upon request.

Table 1. Summary of epidemiologic studies on ALS

Author (ref)	Region	Year(s)	Incidence (/100,000)	Prevalence	Time to diagnosis (mo)	Survival	Age of onset	M:F ratio	spinal onset (%)	Familial (%)
Neilson ²⁴ 1993	France	68 90	1.1* 1.9*							
Bettoni ¹⁴ 1994	Italy / Parma	60-90	0.98	2.5 (1981)		mean 30mo	60	1.2	62	
Giagheddu ¹⁷ 1993	Italy / Sardinia	57-90	0.68	2.26 (1985)		median 30 mean 36	56	1.8	51	
Chió ⁵ 1992	Italy / Piemonte							1.6		
Chió ¹⁵ 1993	Italy	58-87	0.68					1.4*		
Tynes ²⁷ 1991	Norway / Hordaland	79-88	1.6* (0.77-2.8)	3.67 (1988)	mean 30	median 28	61	1.3	51	
Scottish Group ²⁶ 1992	Scotland	89	2.24							
López- Veiga ²² 1988	Spain / Cantabria	74-85	1.01	3.52	median 11	mean 26.6mo 60% 24mo	58M 64F	1.78	61	
Veiga- Cabo ²⁸ 1997	Spain	51-90	1.49*							
Stallones ²⁵ 1989	USA / Kentucky	59-61 64-67 68-78 79-84	0.4 M1.05/F0.56* M1.08/F0.58* M1.23/F0.76*					1.79 1.86 1.62		
Lee ¹³ 1995	USA/ Texas	85-88**				median 21.3	59.5	1.1	59	2.1
Haverkamp ¹⁸ 1995	ALS Clinic database/ Baylor College	83-95				Mean 33.6 median 29.1	55.7	1.7	75	9.5
Mc Guire ⁴ 1996	USA / Western Washington	90-95	1.8 crude 2.1M/ 1.9F*				57M 65F	1.2		
Longstreth ²¹ 1998	USA / Washington & others	90-94						1.2		
Larreatgui ¹⁹ 1988	Panama	74-85					41-50	1.2		
Mitchell ²³ 1990	UK / Lancashire & South Cumbria	76-86	1.86					1.6		
Lima ⁷ 1883	Brazil / Rio de Janeiro	65-74	0.3-0.9					1.1		
Gomes ⁸ 1991	Brazil / Rio de Janeiro	79-86	0.4					1.7		
Almeida Silva ¹⁰ 1998	Brazil / São Paulo	NS						1.7	78	4
Lima ²⁰ 1998	Brazil/ Rio de Janeiro	NS						1.0	61	4
Moraes ⁹ 1998	Brazil / São Paulo	91-94 95-97	0.2-0.32 0.36-0.41							
Castro- Costa ¹¹ 1999	Brazil/ Ceará	80-99				Mean 30	43	1.8	91	

*age-adjusted; **time of diagnosis; M, male; F, female; NS, not specified.

All doctors were mailed a "recall" letter, reminding them of the survey, as well as an interim report. The study ended in April 1999, and a final report was issued to all participating physicians in June 1999.

Descriptive statistics were used for demographic data. Chi-square test was used to test the null hypothesis of independence for onset form according to gender.

RESULTS

One hundred and sixty-eight neurologists sent 540 forms on 511 patients (duplicate forms were eliminated). Of those, 443 meeting the criteria of "probable" or "definite" ALS were analysed.

Two hundred and fifty nine patients (58,5%) were male, yielding a male to female ratio of 1.4/1. One hundred and thirty (29,3%) were born in the state of São Paulo (SP) and 10.4% in the state of Rio de Janeiro (RJ), the 2 most populous states (Fig 1). Twenty-one (4.7%) were born outside the country. It is worth noticing that 202 (45.6%) of the patients were followed in SP, and 60 (13,5%) in RJ, which may reflect the higher concentration of referral centers and physicians in these states.

Two hundred and fifty-nine (58.5%) were followed at private clinics, 178 (51.5%) at hospitals.

Mean age of onset was 52 years old (SD±13), median 52. Age distribution at time of onset shows a higher frequency at ranges 50 to 54 and 55 to 59 years old (14 and 12.4%, respectively). Eighty (18.1%) of the patients presented their first symptoms under the age of 40 (Fig 2).

Of the 443 patients, 380 (85.8%) had definite, and 63 (14.2%) probable ALS.

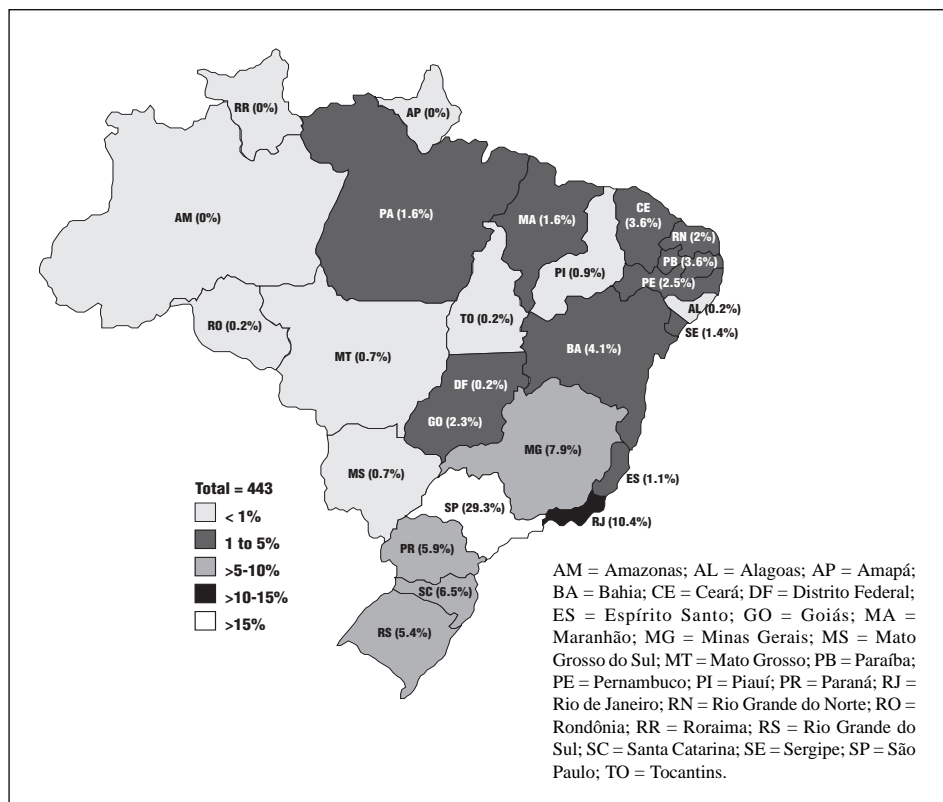


Fig 1. Patient distribution according to place of birth.

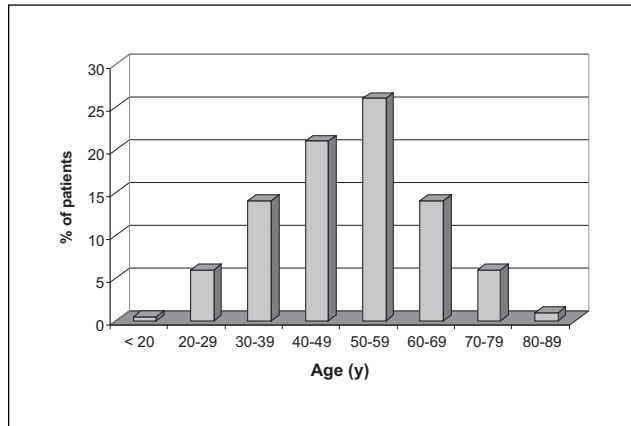


Fig 2. Age of onset. $n = 443$.

Table 2. Sex distribution according to clinical form, time from first symptoms to diagnosis, age of onset and survival.

Characteristic	Male	Female	All
Clinical form*	N (%)	N (%)	N (%)
Bulbar	38 (15)**	44 (24)**	82 (18.5)
Limb	187 (73)	118 (65)	306 (69.1)
Both	32 (12)	20 (11)	52 (11.7)
Time from 1 st symptoms to diagnosis (months)			
Mean (\pm SD)	17 (30)	20 (25)	18 (28)
Median	10	12	11
Range	0-332	0-210	0 to 332
Age of onset (years)			
Mean (\pm SD)	50 (13)	54 (13)	52 (13)
Median	51	54	52
Survival (23 patients) (months)	N = 13	N = 10	
Mean (\pm SD)	49 (46)	33 (18)	42 (37)
Range	7 to 60	9 to 191	7 to 191

*Data missing on 3 patients

** $p < 0,05$

Spinal onset was the most frequent clinical form, present in 306 (69%) of the patients. Of note, spinal onset occurred more frequently in men than in women (73% vs 65%, $p=0,045$) (Table 2).

Time from first symptoms to diagnosis varied widely: from 0 to 332 months (Table 2).

Distribution according to inheritance and age is shown in Table 3.

Electroneuromyography was the most performed test: 416 patients (94%) (Figure 3).

Only 23 (5,2%) deaths were reported (6 in bulbar, 13 in spinal and 4 in generalized onset). Time from first symptoms to death ranged from 7 to 191 months, and there was a trend towards a shorter survival among bulbar patients (median 23 vs 32 months in spinal ALS) (Table 4).

Table 3. Mean age of onset in familial and sporadic cases

“Inheritance”	Sporadic	Familial
Age of onset (y)		
Mean (\pm SD)	52 (13)	47 (13)
Median	53	45
Number of patients (%)*	403 (91)	26 (5.9)

*Data missing on 14 patients

Table 4. Survival in bulbar and spinal patients according to type of onset (N = 19 patients)

Type of onset	Spinal	Bulbar
Survival (mo)		
Mean (\pm SD)	48 (46)	32 (22)
Median	32	23
Range	9-191	7-54

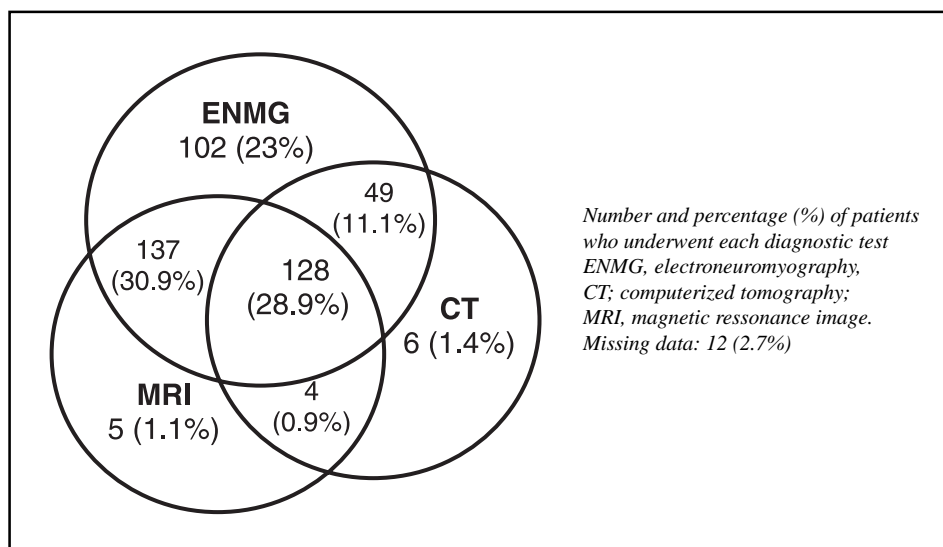


Fig 3. Tests performed.

DISCUSSION

Regional published data concerning ALS mortality in Brazil, where it is fairly reliable (São Paulo and Rio de Janeiro cities), infers an incidence rate of 0.3-0.5/100,000 population. Considering the mean duration of the disease to be 3 years (Table 1), this yields a disease prevalence of about 1,440 to 2,400 cases in Brasil (0.9 to 1.5/100,000 inhab), lower than that described in Europe and USA. The patient population under analysis in this study represents roughly one-fifth to one-third of the ALS population in the country, from referral centers as well as private practices, which helps avoiding biases.

There is no data about the exact number of neurologists practicing in Brazil. Federal Medical Council acknowledges some 4,500 neurologists, but this is an estimate. More than 3,500 neurologists were notified of the study, but participation was voluntary.

Most disease and demographic characteristics (such as earlier onset in the familial form, male-to-female rates, survival, type of onset) in this study are similar to those observed in other countries as well as in other Brazilian studies (Table 1)^{3,4,7-11,13-28}.

The shorter survival time in bulbar onset is consistent with the published literature, and as women had bulbar onset more frequently than men, this may explain why time from first symptoms to death was shorter for females. Nevertheless, drawing conclusions from the small number of patients whose death was reported (23 patients) may be hazardous. Still, the higher rate of bulbar onset among women has not, to our knowledge, been described before, and it may be a Brazilian peculiarity.

ALS's most frequent age of onset, in this sample, is 50-60 years old, with a median of 52. In European countries, ALS's first symptoms occurs more frequently between 59 and 65 years old. This difference is probably due to the different age stratification of our population, younger than the European and American ones. If we calculate the study prevalence in each age strata using the Brazilian population distribution in 1997, the age of onset peaks between ages 65 and 74 (the same as in other countries)¹⁶. In spite of that, we cannot overemphasize the need to consider the possibility of an ALS diagnosis in a relatively young patient: half the patient population is less than 52 years old when first symptoms occur.

Using São Paulo city's ALS-related mortality as an index of Brazil's mortality, the approximate crude incidence rate in Brazil is 0.4/100,000. The crude prevalence would be about 1.2/100,000, and the total number of patients in Brazil, 1,920. Using the US 1994 population as a standard and the age-adjusted "study prevalence", if we had the same age distribution as in the US, 1011 patients would be in the study, and there would be circa 8,300 patients in the country, yielding an age-adjusted prevalence of 5.2/100,000, and an age-adjusted incidence of 1.7/100,000, still lower than the US incidence, which is approximately 2/100,000^{3,29,30}.

We have to bear in mind that age distribution in São Paulo is not the same as in the rest of the country¹⁶. In São Paulo, the older strata are over-represented, which may lead to an over-estimation of the Brazilian incidence.

Although age-adjusted mortality due to ALS is increasing worldwide, a French study based on Grompetzian analysis showed this increase is rather due to disease competition than to change in environmental factors. That is, people are dying from ALS because they are not dying from other diseases²⁴. As therapeutic progress is slow, the social burden due to the disease is bound to increase.

Not surprisingly, ENMG is still an essential diagnostic tool, and MRI is progressively replacing CT as it allows better differentiation from other diseases, thus shortening the time to diagnosis³¹.

The study's major limitation is the possible bias created by voluntary participation. As we do not have precise mortality data, we also have very little background against which to compare our results. This is one of the reasons why patients whose disease classification was "possible", "suspect" (according to El Escorial criteria) or was not specified, were not included in this analysis: in order to limit misdiagnosis, an ever-present problem in ALS^{32,33}.

The sample analysed is numerically significant, considering the disease's relatively low incidence. It is the largest cohort analysed to date in Brazil, and the inclusion of referral centers' as well as private clinics' data reinforce the reliability of the results.

Conclusions

Even though at first glance ALS seems to behave differently in Brazil than it does in Europe and North America, it now appears that the differences between are small. Except for lower age of onset in Brazil, due to difference in age stratification, and for a higher incidence of bulbar onset

among women, in every other aspect encompassed here, it shows the same clinical pattern as in European and North-American countries. More epidemiologic studies are needed in order to assess other variables, such as disease duration and management, which were outside the scope of this study.

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