ORIGINAL ARTICLE

Mortality associated with periodic limb movements during sleep in amyotrophic lateral sclerosis patients

Mortalidade associada aos movimentos periódicos de membros durante o sono em pacientes com esclerose lateral amiotrófica

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ABSTRACT

Objective: To describe the prevalence and severity of periodic limb movements during sleep in amyotrophic lateral sclerosis patients and to explore this fact as a predictor of severity of the condition with respect to mortality. **Methods:** In this case-control study, questionnaire and polysomnographic data were analyzed from 35 amyotrophic lateral sclerosis patients. Controls were matched by age, genre, and body mass index. A Kaplan-Meier curve was used to compare the survival time of patients with periodic limb movements of sleep index below or above 5**. Results:** The number of amyotrophic lateral sclerosis patients with an index greater than five was higher than controls (19 (53%) *versus* 4 (11%); p<0.0001), and the mean index was higher (23.55±40.07 *versus* 3.28±8.96; p=0.0009). Earlier mortality was more common in patients with more than five periodic limb movements per hour of sleep than patients with less than five periodic limb movements per hour of sleep (7/19 (37%) *versus* 1/16 (6%); p=0.04) in this group of patients that had a mean survival of 33 months. **Conclusions**: There were more periodic limb movements of sleep in amyotrophic lateral sclerosis patients than in the control population. The higher number of these movements in amyotrophic lateral sclerosis patients correlates with disease severity and may suggest poor survival.

Keywords: Amyotrophic lateral sclerosis/complications; Quality of life; Restless leg syndrome; Nocturnal myoclonus syndrome; Sleep disorders; Mortality

RESUMO

Objetivo: Descrever a prevalência e a severidade dos movimentos periódicos de membros durante o sono nos pacientes com esclerose lateral amiotrófica e explorar isso como um preditor de severidade da doença e mortalidade. **Métodos:** Estudo caso controle em que foram analisados 35 pacientes por questionários e polissonografia. Os controles foram pareados por idade, gênero, e índice de massa corporal. Uma curva de Kaplan-Meier foi usada para comparar o tempo de sobrevida em pacientes com índice de movimento periódico de membros durante o sono acima e abaixo de 5. **Resultados**: O número de pacientes com esclerose lateral amiotrófica com índice de movimentos periódicos de membros durante o sono acima de cinco foi maior do que os controles (19 (53%) *versus* 4 (11%); p<0,0001) e a média do índice de movimentos periódicos de membros durante o sono também foi maior no grupo dos pacientes (23,55±40,07 *versus* 3,28±8,96; p=0,0009). A mortalidade precoce foi mais comum em pacientes com mais que cinco movimentos durante o sono por hora do que pacientes com menos do que cinco movimentos durante o sono por hora (7/19 (37%) *versus* 1/16 (6%); p=0,04). Nesse grupo, os pacientes tiveram sobrevida média de 33 meses. **Conclusão:** Houve um maior número de movimentos periódicos de membros durante o sono em pacientes com esclerose lateral amiotrófica do que na população controle. O maior número de movimentos periódicos de membros durante o sono em pacientes com esclerose lateral amiotrófica foi correlacionado com severidade da doença e pode sugerir menor sobrevida.

Descritores: Esclerose amiotrófica lateral/complicações; Qualidade de vida; Síndrome das pernas inquietas/mortalidade; Síndrome da mioclonia noturna/mortalidade; Transtornos do sono; Mortalidade

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting two to three people per 100.000 in the general population. It involves upper and lower motor neurons, typically resulting in death 3 to 5 years after onset[1,2]. The interest in sleep of ALS patients has increased in recent years. Early management of respiratory abnormalities during sleep in ALS patients can improve quality of life[3].

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A relation between ALS functional impairment and restless leg syndrome (RLS) was recently established[4,5]. The association between RLS and periodic limb movements of sleep (PLMS) in neurodegenerative diseases is notable. Patients with Parkinson's disease (PD) have an increased prevalence of RLS and PLMS[6]. An increase in PLMS has recently been described in a subsample from a larger study of ALS patients[7,8].

PLMS have been studied in systemic diseases including renal failure[9], in which they are associated with difficulty initiating and maintaining sleep, impaired quality of life, poor health, increased cardiovascular risk, and predicted earlier mortality[10-14].

OBJECTIVE

The goal of this study was to describe the prevalence and severity of PLMS in ALS patients and to explore this as a predictor of severity of the condition with respect to mortality.

METHODS

The inclusion criteria were ALS patients (upper and lower neurons involved) referred to investigate the possible requirement of nocturnal ventilatory support, between 2009 and 2010, at Sunnybrook Hospital, Toronto, Canada, who were not previously on bilevel positive airway pressure (BiPAP) at the time of presentation to the laboratory, and had signed the consent form. The exclusion criteria were patients with other differential diagnosis and patients who refused to participate in the study. Of 53 ALS patients who had sleep studies, 37 provided consent for research. One patient did not achieve sleep in the laboratory. Another patient was removed after confirmation of other diagnosis. Data were therefore analyzed for a total of 35 patients. Information was collected about ALS subtype (bulbar *versus* limb onset) and use of riluzole.

The control group consisted of an equal number of patients from the sleep clinic, who were mainly referred for suspicion of sleep apnea, without neurological complaints or symptoms. They were matched for age, genre and body mass index. Self-reported anemia, diabetes, and polyneuropathy were also matched between groups. None of the controls or patients reported taking dopaminergic medications, gabapentin, and pregabalin. Within the ALS group, subjects were dichotomized to assess differences between ALS patients with PLMS (PLMS index >5) and without PLMS (PLMS index <5).

Clinical data from the chart and a sleep habit questionnaire were utilized. Daytime sleepiness was assessed using the Epworth Sleepiness Scale[15]. The assessment of RLS was based on a questionnaire that was completed by patients or caregivers[16,17]. The ALS severity was determined using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)[18]. The scores reported are the fully completed scale closest to the sleep study for each patient.

Patients were submitted to spirometry (Vmax spectra V20c, Sensormedics Inc, Yorba Linda CA, USA). Upright forced vital capacity (FVC) was checked close to the sleep study[19].

Patients underwent conventional nocturnal polysomnography that was scored according to the 2007 American Academy of Sleep Medicine (AASM) guidelines[20]. Sleep architecture including sleep efficiency, and percentages of N1/N2/N3/REM sleep were compared between controls and ALS patients. A nasal pressure transducer was used to assess airway resistance. The frequency of obstructive and central apneas per hour during sleep was compared. The apnea-hypopnea index (AHI), defined as the number of apneas or hypopneas with >4% oxygen desaturation per hour of sleep was compared. To control for outliers, the number of patients with an AHI>5 was also analyzed. The respiratory disturbance index (RDI), defined as the frequency of all respiratory events including apnea, hypopnea and respiratory-event-related arousals per hour of sleep was also used to assess all respiratory related sleep disruption. Oxygen saturation was measured using pulse oximetry. Lowest oxygen saturations were compared between groups. The PLMS index was scored precisely according to the AASM[21].

The institutional research ethics board approved the protocol and patients, as well as controls, provided written informed consent.

Statistical analysis

Normal distribution of variables was verified using a Kolmogorov-Smirnov test. The χ^2 test or Fischer's test were used to compare qualitative variables. A one-tail Student's *t*-test or Mann-Whitney U test for independent samples were used to compare quantitative variables. Statistical significance was considered for $p<0.05$ with Bonferroni correction for multiple comparisons. A Kaplan-Meier curve was used to compare the survival time between patients expressing a PLMS index below or above 5. Time to endpoint was considered the time

from symptom onset to all-cause mortality as of January 7, 2011.

RESULTS

Comparisons between ALS patients and controls are shown in table 1. The PLMS index was higher in ALS patients than in control patients (23.55±40.07 *versus* 3.28±8.96; p=0.0009); and many ALS patients had a PLMS index >5 (19 (54%) *versus* 4 (11%); p<0.0001). There was no difference in limb movement arousal index between ALS patients and controls. There was no difference in the AHI, number of patients with an AHI>5, or RDI between groups. As expected, ALS patients had a lower nadir oxygen saturation (83.51±7.48 *versus* 86.80±4.99; p=0.02). There were no significant differences in sleep architecture, Epworth Sleepiness Scale scores, and self reported RLS symptoms when comparing the ALS and control groups.

The observed ALS patient survival period ranged from 13 to 119 months with a mean of 32.69±21.28 months. Within the ALS group, there were 19 ALS patients with PLMS index >5, and 16 with PLMS index <5. As shown in figure 1, mortality was higher in patients

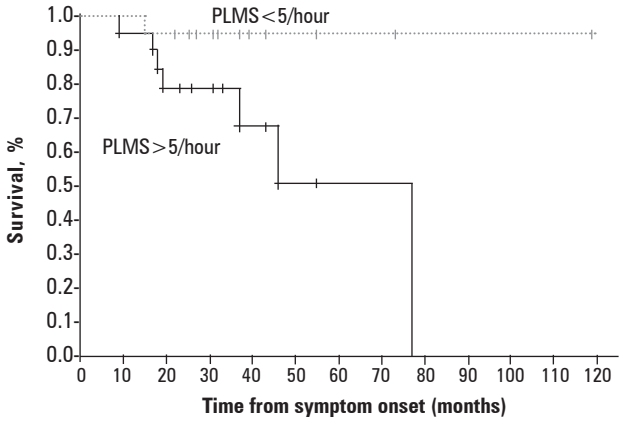

Figure 1. Kaplan-Meier survival curve of patients with periodic limb movements – lower (PLMS>5) and higher (PLMS<5)

Table 1. Clinical and sleep characteristics of controls and ALS patients

Characteristics	Controls (n=35)	ALS (n=35)	p value
Age	61.83±12.66	64.03±12.70	0.23
Sex (Male)	19 (54%)	19 (54%)	0.5
Body Mass Index	25.62±3.37	24.25±4.66	0.08
Anemia	2/35 (6%)	2/35 (6%)	0.5
Diabetes	1/35 (3%)	3/35 (9%)	0.14
Polyneuropathy	0/35 (0%)	1/35 (3%)	0.5
Epworth Sleepiness Scale	6.67±4.42	8.00±4.66	0.12
Periodic Limb Movements (Self report Questionnaire)	12/35 (34%)	4/35 (11%)	0.01
Restless Sensation	13/34 (38%)	13/31 (42%)	0.09
Sleep Efficiency	69.59±18.12	62.62±18.10	0.06
Percent N1	17.50±8.66	16.67±14.98	0.39
Percent N2	56.67±11.77	54.00±12.85	0.18
Percent N3	10.83±11.62	14.97±12.93	0.08
Percent REM	15.02±6.92	14.40±8.07	0.37
Apnea Hypopnea Index	8.08±12.82	9.96±14.34	0.38
Respiratory Disturbance Index	13.15±15.47	14.69±17.56	0.39
Individuals With AHI>5	11/35 (31%)	15/35 (43%)	0.16
Lowest SaO2	86.80±4.99	83.51±7.48	0.02
Limb Movement Arousal Index	1.84±3.54	4.11±9.44	0.14
Periodic Limb Movement Index (PLMI)*	3.28±8.96	23.55±40.07	<0.001
Number of Individuals With PLMI >5*	4/35 (11%)	19/35 (54%)	<0.001

Values reported as mean ± standard deviation or as a whole number followed by percentage in parentheses.
*Statistically significant after Bonferroni correction.
ALS: amyotrophic lateral sclerosis; BMI: body mass index; AHI: apnea-hypopnea index; PLMI: periodic limb movement index.

Table 2. Clinical and sleep characteristics of patients with periodic limb movements less than and higher than five per hour

Characteristics	<5 Periodic Limb Movements/Hour (n=16)	>5 Periodic Limb Movements/Hour (n=19)	p value
Age	60.31±13.46	67.16±11.45	0.06
Sex (Male)	11/16 (69%)	8/19 (42%)	0.06
BMI	25.16±5.78	23.49±3.45	0.15
Time symptom onset to diagnosis (months)	16.75±16.72	15.79±16.69	0.43
Bulbar Onset	3/16 (19%)	9/19 (47%)	0.04
Upper Limb Onset	8/16 (50%)	6/19 (32%)	0.11
Lower Limb Onset	5/16 (31%)	4/19 (21%)	0.25
Forced Vital Capacity (% predicted value)	61.76±21.69	52.52±24.22	0.12
ALSFRS-R score	32.97±7.83	27.31±10.33	0.05
Riluzole Use	10/16 (62%)	13/19 (68%)	0.36
BIPAP Used	8/16 (50%)	9/19 (47%)	0.43
Epworth Sleepiness Scale	9.57±4.50	6.78±4.53	0.05
Leg Cramps	5/16 (31%)	12/18 (67%)	0.02
Sleep Efficiency	61.11±21.93	63.89±14.64	0.33
Percent N1	19.51±19.43	14.28±9.81	0.15
Percent N2	50.73±14.72	56.76±10.67	0.08
Percent N3	12.63±10.35	16.93±14.76	0.17
Percent REM	17.17±8.31	12.07±7.27	0.03
Apnea Hypopnea Index	16.97±18.20	4.06±5.65	0.0030
Respiratory Disturbance Index	22.94±22.26	7.74±7.60	0.0043
Individuals with AHI>5	9/16	6/19	0.07

No differences were statistically significant after Bonferroni correction.
PLMS: periodic limb movements of sleep; BMI: body mass index; FVC: forced vital capacity; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; AHI: apnea-hypopnea index; RDI: respiratory disturbance index.

with PLMS >5 per hour than patients with PLMS <5 per hour (7/19 (37%) *versus* 1/16 (6%); p=0.04).

The analysis of patients with PLMS index below and above 5 is summarized in table 2. The ALSFRS-R score tended to be higher in patients with PLMS <5 per hour (32.97±7.83 *versus* 27.31±10.33; p=0.05)[18]. Patients with PLMS <5 per hour tended to score higher in the Epworth Sleepiness Scale (9.57±4.50 *versus* 6.78±4.53; p=0.05). Conversely, cramps tended to be more prevalent among patients with PLMS >5 (12/18 (67%) *versus* 5/16 (31%); p=0.02).

DISCUSSION

This study demonstrated that a PLMS index higher than 5 was more prevalent in patients with ALS than in a control population. Given the recent finding that RLS is more common in patients with ALS, it is expected that the closely associated PLMS would also be increased, which we have confirmed in this population[4].

The group with more PLMS actually tended to have a lower Epworth Sleepiness Scale score and was subjectively more alert. A higher incidence of PLMS is implicated in insomnia and fragmented sleep, which are associated with a higher cardiovascular risk[21].

A few limitations of this retrospective study must be highlighted. Many confounding factors in ALS mortality, such as lower ALSFRS-R scores, lower FVCs, cramps, and bulbar onset were more prevalent in patients with PLMS higher than 5.

PLMS may be seen in the context of oxidative stress seen in ALS. Interestingly, dexpramipexole, a dopamine agonist, is currently being developed as a treatment for ALS, for it is thought to reduce oxidative stress[22,23]. Dopamine agonists are first line treatment for RLS and PLMS[24].

CONCLUSION

The association of PLM and higher mortality of ALS patients will require confirmation and could simply represent more advanced disease. Further investigations are required to better characterize this relation and determine its significance, considering that interventions that reduce PLMS may benefit patients with ALS.

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