Periodic Limb Movements in Tetraplegia

Abstract

Objective

To establish the prevalence of Periodic Limb Movements during Sleep (PLMS) in tetraplegia, controlling for obstructive sleep apnoea. To explore whether demographic and injury characteristics affect PLMS.

Study Design

Retrospective cohorts

Setting and Participants

173 participants with acute (<12 months) and 92 with chronic (>12 months) tetraplegia who underwent full overnight diagnostic sleep studies.

Interventions and outcome measures

262 sleep study recordings were included. A randomly selected subgroup of 21 studies was assessed for PLM during wakefulness. Data were analysed according to the current American Academy of Sleep Medicine guidelines.

Results

41.6% of participants (43(15.7) years and 14.9% female) had a motor and sensory complete lesion. Sleep was poor with both OSA (87.8% with apnoea hypopnoea index$\geq$5) and PLMS (58.4% with PLMS per hour PLMSI>15) highly prevalent. There was no difference in the PLMSI between those with OSA (36.3(39.8)) or without (42.2(37.7), P = 0.42). PLMS were evident during REM and NREM sleep in all of the 153 patients with PLMSI>15. All 21 participants in the subgroup of studies analysed for the PLM during quiet wakefulness, exhibited limb movements. None of the modelled variables (injury completeness, gender, OSA severity or time since injury) significantly predicted a PLMSI>15 (P = 0.343).

Conclusion

In conclusion, this study confirms the high prevalence of PLM in tetraplegia and the presence of leg movements in NREM and REM sleep along with wakefulness after controlling for OSA. No associations between the presence of PLMS and patient characteristics or injury specific aspects were found.

Keywords

Disclosure statement

The authors declare they have neither relevant financial disclosures nor conflicts of interest.

INTRODUCTION

Sleep problems are frequently reported in people with a spinal cord injury (SCI).[1-3] It appears that obstructive sleep apnoea (OSA) is the predominant disorder in tetraplegia,[2] whereas muscle spasms and somatic disturbances such as pain and paraesthesia additionally contribute to sleep disturbance in paraplegia and incomplete lesions.[1]

Periodic Limb Movements are a sleep related movement disorder first described by Lugaresi *et al* in 1972.[4] The movements are characterized by episodes of repetitive and highly stereotyped periodic limb movements that occur during sleep. These movements may be related to arousals, obstructive sleep apnoea (OSA) and awakenings[5] and can therefore negatively impact sleep efficiency.

Periodic Limb Movements of Sleep (PLMS) are indexed per hour to provide the periodic leg movement of sleep index (PLMSI). Excluding those with significant OSA, the prevalence of an elevated PLMSI in the general population is 7.6%.[6] In the able-bodied population, PLMS typically occur during Non Rapid Eye Movement (NREM) sleep only and have a clear periodicity.[7] This contrasts with SCI where PLMS are highly prevalent in those with lesions above T10,[8-10] not always clearly periodic and observed throughout quiet wakefulness and REM.[11] These SCI data are however limited in their sample sizes and inconsistent in their sampling and findings.[7,10]

Confounding these previous data is the issue of OSA in SCI. Leg movements are frequently associated with apnoea termination and arousal from sleep. To address this, the American Association of Sleep Medicine (AASM) scoring rules exclude events that occur during a period from 0.5 seconds prior to an apnoea or hypopnoea to 0.5 seconds following a scored respiratory event.[12] Obstructive sleep apnoea is apparent within weeks of cervical SCI (tetraplegia),[13,14] is 2-5 times more prevalent than in the general population[2,15] and is associated with significant symptoms and reduced quality of life.[3] Some PLMS in SCI studies have excluded OSA,[10] others have included participants with OSA and used the AASM rules to exclude PLMS adjacent to respiratory events,[11] while some authors make no reference to possible co-existent OSA.[8,9] To address these limitations in the previous literature and to explore factors that are potentially related to PLMS in tetraplegia we analysed a large sample of polysomnographic records collected in previous sleep research in tetraplegia.[2,16] This analysis aims to: characterise PLMS in a large sample of people with traumatic tetraplegia resulting from a cervical SCI who have undergone polysomnography (PSG), to confirm PLMS across REM, NREM and wake in tetraplegia and to explore whether the presence of OSA, demographic and injury characteristics were related to the prevalence or severity of PLMS.

SUBJECTS AND METHODS

Subjects

Polysomnographic sleep recordings collected from 92 people with chronic (>12 months) tetraplegia who participated in previous, community based research between July 2007 and March 2008 at Austin Health[2] and 173 people with acute (<12 months) tetraplegic injuries, previously enrolled in the 'Continuous positive airway pressure for obstructive sleep apnoea in quadriplegia' (COSAQ) trial[16] between September 2009 and February 2013. Both studies were approved by the Austin Health Human Research Ethics Committee. The polysomnographic data were collected for acute and chronic participants after an average of 0.28 (SD=0.16) and 12.32(7.76) years, respectively, from the SCI. The full description of the sampling strategy and inclusion, exclusion criteria can be found in the original references[2,16]. For this current analysis, participants were excluded if there was technical failure of the limb movement signal on the PSG or if demographic data were unavailable. Demographic data were obtained from clinical trial and hospital medical records. The level and completeness of the lesion were assessed by the International Standards for Neurological Classification of SCI (ISNCSCI).

Polysomnographic sleep recording

Each participant underwent overnight PSG (Compumedics SomtePSG, Abbotsford, Australia) carried out in patients' homes (chronic) or on inpatient wards (acute) as per original study protocols. The PSG consisted of two central electroencephalographic (EEG) channels, bilateral electrooculography (EOG), submentalis muscle electromyogram (EMG), electrocardiogram (ECG), nasal cannulae for flow, abdominal and thoracic bands for respiratory effort. Limb movements were detected using a piezoelectric sensor on the left and right dorsum of each foot and recorded via a single, combined channel. The leg sensors detect movement *per se*, not muscle EEG activity. Data were analysed using Compumedics ProfusionPSG 3 version software.

Scoring of the PSG and the detection of the Periodic Limb Movements

The PLMS were scored and summarized per hour of sleep according to the American Academy of Sleep Medicine (AASM) criteria to generate the PLMSI.[12] Specifically, PLMS were scored when at least four consecutive leg movements during a period of sleep were identified with each movement lasting 0.5-10 seconds and an onset to onset interval of 5-90 seconds. Consecutive leg movement recordings within 0.5 seconds were counted as one. A PLMS was not scored if it occurred with 0.5 seconds of the commencement or the termination of an apnoea or a hypopnoea. Sleep was staged, respiratory events and arousals scored according to current AASM guidelines.[12,17] A PLMSI of greater than 15 was considered pathological.[6] To determine if there was any effect of the progression of sleep on PLMSI, the PLMSI was calculated separately for each quartile of the night in a second, randomly selected subset of 29 participants.

The leg movement indices were also calculated during wake in a randomly selected subgroup of 21 participants who fulfilled the criteria of having more than 10 minutes of quiet resting prior to sleep onset and after awakening. The periodic leg movement index during wakefulness (PLMWI) was obtained from and time-weighted averaged from three segments of PSG; 30 minutes before the first sleep onset, 30 minutes after sleep offset (morning awakening) and 30 minutes within the longest period of wake after sleep onset. If the wake after sleep onset segment was less than 30 minutes, the longest available segment was scored provided at least 10 minutes of data were available.

Statistical analyses

Descriptive statistics (mean and standard deviations (SD)) were calculated for all groups. parametric (Student t-test) and non-parametric (Chi squared test) analyses were performed to assess differences between the acute and chronic participants and between those with and without OSA. A conservative apnoea hypopnoea index (AHI) of less than five events per hour was used as the initial cut-off for categorization of "no OSA". A less conservative cut-off of AHI < 15 was also calculated to facilitate comparison with data from previous publications on the prevalence of PLMSI > 15/hour in the general, able-bodied population.[6] The population data were plotted alongside the mean and 95% CI of the SCI sample and proportions compared with the chi-squared statistic. Multivariate logistic regression analysis was performed to test for associations between the presence of PLMSI and sex, AHI, age, injury severity (motor and sensory complete versus incomplete) and time since injury. The distribution of PLMSI across the night (quartiles) were compared using a univariate repeated measures analysis of variance and univariate Pearson r correlations were performed to examine the relationships between the arousal index (AI), PLMSI and AHI.

RESULTS

All of the chronic participants' studies were able to be fully analysed, but three of the acute studies were excluded due to technical failures of the leg recording leads. The spinal lesion levels of injury ranged from C1 to T1 and injury severity from ISNCSCI (International Standards for Neurological Classification of SCI) A to D.

Those with chronic injuries had their injuries on average over 12 years earlier than the acute cohort, were older, twice as likely to be women and more likely to have complete injuries. No significant differences were observed in PLMSI, proportions with PLMSI > 15 events per hour, OSA severity or prevalence between the acute and chronic samples. Obstructive sleep apnoea prevalence (AHI $\geq$ 5) was extremely high at over 85%. The significant demographic differences were expected as a consequence of the samples pooled for this study. The outcome variables of primary interest (PLMSI and OSA/AHI) were not different across the acute and chronic cohorts and as such, data were pooled for subsequent analyses.

Table 1 – Demographic and Objective Data for the SCI groups

	Acute (n=170)	Chronic (n=92)	P value
Mean (SD) age	41.6 (13.0)	46.0 (16.8)	0.03
% female	10.0%	24.2%	0.002
% Complete (ISNCSCI A)	37.0%	50.0%	0.04
Mean time since injury (years)	0.28 (0.16)	12.2 (7.74)	<0.000
Mean PLMSI	36.2 (36.8)	38.4 (44.2)	0.67
% PLMSI > 15	58.8%	57.6%	0.85
Mean AHI	29.7 (23.3)	29.5 (24.3)	0.93
% OSA (AHI > 5)	88.2%	87.0%	0.76

ISNCSCI A - International Standards for Neurological Classification of SCI, motor and sensory complete lesion, AHI = Apnoea hypopnoea index

Table 2 – Sleep summary statistics.

	Mean	SD	Min-Max
Total sleep time (min)	358.2	96.5	34.5-583.5
Wake after sleep onset (min)	105.9	74.6	5-434.5
AHI	29.7	23.6	0-122.7
PLMSI n = 262	37.0	39.5	0-234.9
PLMSI NREM n = 262	38.4	42.9	0-253.7
PLMSI REM n = 262	28.4	34.3	0-166.8
PLMSI (AHI $\leq$ 5) n = 32	42.2	37.7	0-156.2
PLMSI (AHI $\leq$ 15) n=92	37.7	35.6	0-156.2
AI	22.4	15.2	2.1-107.8
REM latency (min)	101.5	69.8	1-464.5
N1 (% TST)	11.1	9.5	0.42-60.2
N2 (% TST)	48.3	11.9	18.4-87.4
N3&N4 (% TST)	85.6	50.3	0-264
REM (% TST)	17.2	7.2	0-41.2

AHI = apnoea hypopnoea index, REM = rapid eye movement sleep, NREM = non-rapid eye movement sleep, N1 = stage one sleep, N2 = stage two sleep, N3&N4 = stage three and four (slow wave) sleep, REM latency = time to first REM after sleep onset, TST = total sleep time, OSA = obstructive sleep apnoea, PLMSI = periodic leg movement sleep index (events per hour),

Sleep was poor in the sample overall (Table 2) with both OSA and PLMS highly prevalent. At least mild OSA (AHI $\geq$ 5) was present in 87.8%, moderate OSA (AHI $\geq$ 15) in 64.9%, PLMS (PLMSI > 15) in 58.4% and severe PLMS (PLMSI > 29) in 43.9% of the cohort. Overall sleep architecture was poor with a preponderance (almost 50% in both groups) of Stage 2 NREM sleep and REM sleep reduced overall. Ninety seven patients (36.7%) spent less than 15% of TST in REM and in 34 patients (12.9%) the REM sleep was less than 10% of TST. The average arousal index was mildly elevated at 22.4 events per hour.[18]

There was no difference in the PLMSI between those with OSA (AHI $\geq$ 5, n = 230, mean PLMSI (SD) = 36.3(39.8)) or without (AHI < 5, n = 32, 42.2(37.7), P = 0.42). Similarly, OSA had no effect on the proportion of people with a PLMSI > 15 (OSA n = 230, 60%; no OSA n = 32, 50%, P = 0.30). The overall prevalence of PLMSI > 15 in the tetraplegia cohort was 58.4%, statistically significantly higher (p < 0.001) than the able-bodied prevalence of 7.6%.[6] (Figure 1.)

No variation in PLM severity was observed over the course of the night. (Quartile 1 average=49.6 (SD=54), Q2 46.4(53), Q3 55.3(57), Q4 46.1(46.3), F = 0.44, P = 0.72. Of the 153 patients with PLMSI>15, PLMS were evident during REM and NREM sleep in all. All 21 participants in the subgroup of studies analysed for the PLM during resting wakefulness, exhibited limb movements that could be classified according to the criteria detailed in the methods. The average PLM index during wake was 92.9 (SD=52.2) events per hour (Figures 2, 3 & 4).

None of the modelled variables (injury completeness, gender, AHI or time since injury) significantly predicted a PLMSI > 15 (model significance p = 0.343). The variable coefficients (and associated P value) were; motor and sensory completeness -0.18, (P = 0.5); AHI 0.002 (0.72); age (years) 0.01 (0.24); sex (male = yes) 0.68 (0.057); time since injury (years) 0.0058 (0.75). There was a significant correlation between the AHI and the frequency of arousals from sleep (AI, r = 0.61, P < 0.001) but no relationship between PLMSI and the AI (r = -0.07, P = 0.24) or between the PLMSI and the AHI (r = -0.04, P = 0.50).

DISCUSSION

The present study aimed to document the prevalence and severity of PLM during sleep in a large cohort of people with tetraplegia and to examine whether PLM were related to time since injury, obstructive sleep apnoea, lesion level or injury severity. This study confirmed that PLMS are over seven times more prevalent in tetraplegia than in the able bodied population.[6,10] Further, the current study controlled for the highly prevalent confounder of OSA in this same population. The current study data found that the PLMSI was not affected by OSA severity and that the arousal index was associated with the AHI but not the PLMSI.

Leg movements were observed in people with tetraplegia during REM and wake. This finding supports prior studies that have documented leg movements during sleep in SCI patients that continued during wakefulness.[10,11,19] These findings raise the question of whether the leg movements occurring during wake could be classified as Periodic Limb Movements, given that the AASM defines Periodic Limb Movements as occurring only during sleep.[17] In addition, the studies from which these data were derived did not assess restless leg syndrome specific symptoms and as such we are unable to meaningfully differentiate the observed PLM during wake from the restless leg syndrome.

Although the aetiology of PLMS remains unclear, the findings of PLMS in NREM, REM and wakefulness may suggest that PLMS activity is not exclusively triggered by hypothalamic sleep-wake rhythms in SCI patients, as is suggested in the able-bodied. While in the able-bodied, PLMS only appear during NREM, the current finding in SCI supports the suggestion that the movement itself may be derived from spinal cord central pattern generation rather than solely a brain derived signal.[19] In SCI the reflex movements are clearly no longer controlled by the descending axonal pathway inhibitory stimuli, which potentially cause a motor neuron overexpression during all stages of sleep and wakefulness. This is consistent with an inhibitory effect controlled by the hypothalamic sleep-wake rhythm, which in able-bodied, with intact descending axonal pathway, suppresses PLMS during wake and REM.[19]

Findings in radiology and pharmacology have provided indirect evidence of the involvement of the dopaminergic system in the pathogenesis of PLMS and restless leg syndrome.[20] Iron is an essential co-factor for the formation of L-dopa, the precursor of dopamine. Iron deficiency in the multiregional brain, mainly in the substantia nigra, has been shown to correlate with the presence of restless legs,[21] however differences in dopamine and iron-related markers (specifically, a low ferritin) have also been found in the cerebrospinal fluid of restless leg syndrome patients.[22,23] Iron deficient mice and knock out iron-deficient spinal dopamine D(3)-receptor mice support this theory by showing increased locomotor activity resembling restless or PLMS.[24] Whether this mechanism may also play a role in the aetiology of PLMS is still unknown. The high prevalence of PLMS in SCI patients in this study may support this theory, due to a high prevalence of malnutrition, including iron deficiencies, in SCI patients.[25] The current paper was not designed to directly assess this hypothesis however, and as such this remains speculation.

This study has not been able to find a pattern in the appearance of PLMS over the course of the night, supporting previous data that clear periodicity is not always observed in people with SCI and PLM.[7] Additionally, there were no apparent relationships between demographic factors such as gender, age or injury (AIS, severity and time since injury) and the presence of PLMS. This further suggests that the cervical spinal injury *per se* is the causative factor in the tetraplegia population.

Overall, sleep of the participants in the current study was poor, however without a matched control group it is not possible to precisely estimate the difference between the SCI sample and the able-bodied population. Several studies have reported that people with SCI experience substantially worse subjective sleep than their able-bodied counterparts[1,3] and in this study the percentage of wakefulness after sleep onset was approximately 30% of total sleep time compared to 5% in the general population.[26]

The primary potential confounder of the study results remains the up to 78% prevalence of OSA in patients with tetraplegia[16] and associated scoring and attribution of association of the observed PLMS. In reviewing the raw data traces for this project, it was apparent that many of the leg movements were coincident with snoring and respiratory events. As such, these leg movements were unable to be scored as PLMS according to the AASM rules.[17] This would be expected to underestimate the PLMSI, yet the PLMSI was markedly elevated and the PLMSI > 15 category was highly prevalent. The high PLMSI persisted in the subset of participants without OSA; in fact, the PLMSI was higher in those without OSA suggesting that the AASM scoring rules lowered the PLMSI in those with OSA (Fig 2, 3 & 4).

Participants from this study were initially recruited for studies investigating OSA, and the sleep studies were performed without CPAP or other treatments. As such, the clinical significance and impact on daytime function of PLMS in SCI was not able to be addressed directly. The relationships between daytime function and sleep related movement, breathing and circadian disorders are complex in the able-bodied and are only recently being explored after SCI.[3,27,28] Given the multi-factorial nature of sleep disturbances in SCI, it is likely that future research on PLMS should consider specific treatment studies as a method for "unpacking" symptomology. For example repeat studies on continuous positive airway pressure treatment for OSA in tetraplegia may reveal the contribution of an elevated PLMSI to sleep-related daytime symptoms.[29] In the current study, we took the opportunity to add to the literature data from a large cohort of sleep studies, however the original samples were not collected with PLMS prevalence estimation as the primary outcome. People with paraplegia are also excluded from our findings, despite there being evidence that PLMS may also be prevalent in those with lesions from T1 to T10.[9,10]

Only one channel was used to document the leg events detected in both legs. No distinction has thus been able to be made between which leg moved and therefore no data detailing whether the PLMS were bi- or unilateral. Different ratios of mono- and bilateral movements

are reported in various disorders[30] and potentially hemispheric incomplete SCI could provide additional information about PLMS aetiology.

CONCLUSION

In conclusion, this study confirms the high prevalence of PLM in tetraplegia and the presence of leg movements in NREM and REM sleep along with wakefulness after controlling for OSA. No associations between the presence of PLMS and patient characteristics or injury specific aspects were found.

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FIGURE LEGENDS

Figure 1. Prevalence of Periodic Leg Movements during Sleep Index (PLMSI) in the able-bodied and people with tetraplegia.

Proportions and 95% confidence intervals for the able bodied (from Scofield 2008, n = 593)[6] and all of the tetraplegia sample (n = 262) and those with an AHI < 15 (n = 170). Able-bodied participants with sleep apnea as defined by AHI $\geq$ 15 were excluded from the Scofield publication.

Figure 2. Illustration of PLMS during REM sleep

The top pane of the polysomnography is a 30 second time base and the lower 5 minutes. The fine red vertical line indicates the same point on the recording on the upper and lower panels. Note the regular leg movements seemingly unrelated to the apnoeac events and the proximity of a number of leg movements to the start or the end of scored respiratory events (obstructive apnoeas). These PLM events would not be scored or included in the PLMSI.

Figure 3. Illustration of PLMS during stage 2 NREM sleep

Figure 4. Illustration of PLMS during REM and wakefulness

Note the regular PLM that do not appear modified by sleep state (wake or REM) nor by respiratory events.