Chapter 5

Sleep disturbances associated with periodic leg movements in chronic sarcoidosis

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Abstract

Background and aim

Many sarcoidosis patients suffer from fatigue and sleep disturbances. Recently, it was demonstrated that obstructive sleep apnoea (OSA) is rather common in sarcoidosis. Moreover, sheet intolerance and painful legs are frequently reported in sarcoidosis patients. These symptoms might interfere with sleep quality.

Methods

In order to determine the relationship between objective and subjective sleep disturbance full polysomnography, including leg electromyography (EMG) analysis, was performed in 46 chronic sarcoidosis patients indicating awakening unrefreshed in the morning.

Results

In 20 (44%) patients OSA activity [60% with PLM (n=12), 40% without (n=8)] was demonstrated, while in 7 patients (15%) significant periodic leg movement (PLM) without OSA were found. In 19 patients (42%) no OSA or PLM activity was present. Moreover, restless legs (RLS) were reported by 52% of the patients (45% in OSA; 71% in PLM; 47% in others). Distribution of sleep stages and sleep fragmentation was comparable in all groups. In a healthy snoring control group (n=102) a prevalence of PLM was found in 13.7% (17.8% in men; 3.4% in women), while RLS were only reported by 1.4% (men) and 6.9% (women).

Conclusions

Sleep disturbance (OSA and/or PLM) and RLS were demonstrated in more than half of the studied sarcoidosis patients. A high prevalence of RLS or PLM (primary and secondary) has not been reported before in sarcoidosis. Further studies are needed to establish whether RLS, OSA and/or PLM might contribute to fatigue and whether fatigue complaints improve after treatment of RLS/PLM/OSA.

Introduction

Sarcoidosis is a multiorgan inflammatory disorder of unknown origin, characterized by T-lymphocyte and mononuclear phagocyte infiltration in the affected organs, granuloma formation, and distortion of the normal micro-architecture, which is probably antigen-driven.[1] The clinical manifestations of sarcoidosis are largely nonspecific, dependent on the intensity of the inflammation and organ systems affected, of which the lung is the most prominent.

Asymptomatic muscle involvement appears to be quite common, whereas symptomatic muscle involvement is rare.[2,3] Patients with sarcoidosis generally present with symptoms directly related to chest involvement such as coughing, dyspnoea, particularly with exertion, and chest pain. Furthermore, they may suffer from nonspecific constitutional complaints such as fever, weight loss, fatigue, anorexia and malaise.[4-6]

Fatigue appears to be the most frequently reported symptom.[6,7] When features of disease activity, for example radiological abnormalities, lung function impairment and serum angiotensin converting enzyme (sACE) levels become normal, less specific and otherwise difficult to objectify symptoms, such as fatigue, may persist. Besides fatigue many sarcoidosis patients suffer from sleep disturbances.[8,9] Recently, it was demonstrated that obstructive sleep apnoea (OSA) is frequent in sarcoidosis.[10] Prolonged corticoid use could lead to weight gain and myopathy involving the pharyngeal musculature, while severity of the disease, with pronounced muscle involvement, is another possible factor.[11-14] Moreover, sheet intolerance and painful legs are frequently reported in sarcoidosis patients.[15] Small fiber neuropathy has been found to be present in sarcoidosis.[15,16] Symptoms of small fiber neuropathy consist of peripheral pain, paraesthesias, intolerance for bedclothes, hyperhidrosis, hypohidrosis, sicca syndrome, facial flushing, diarrhoea, constipation, micturation disturbances and male sexual dysfunction.[17] Polydefkis et al. found that small fiber neuropathy was also frequently present in patients with late-onset restless legs syndrome.[18] Since restless legs syndrome is frequently associated with periodic leg movement disorder (PLMD), we hypothesized that PLMD is also present in sarcoidosis. No data are known, however, about the frequency of periodic leg movements in sarcoidosis patients. The aim of the present study was to evaluate the relationship between objective and subjective sleep disturbance with emphasis on the occurrence of periodic leg movements (PLM) in sarcoidosis.

Materials and methods

Subjects

Forty-six out-patients suffering from sarcoidosis, who attended the University Hospital Maastricht, were enrolled in this study. All patients suffered from fatigue and indicated awakening unrefreshed in the morning. The diagnosis of sarcoidosis was based on the international guidelines.[1] Subjects with any significant medical history or co-morbidity were excluded from the present study. When polysomnography was performed, 30 patients had been treated with corticosteroids for at least three months, e.g. prednisone orally (initial dose 40 mg daily, decreased by 10 mg a month). Sixteen patients had not been treated during the previous 3 months. 15 patients (33%) were still using oral corticosteroids at the time of the polysomnography. Only 2 of the studied cases were current smokers. The number of pack years for the whole group was 9 (17) years. The diagnosis of sarcoidosis was confirmed 5.2 (5.9) years ago. Clinical characteristics of the patients are summarized in table 5.I.

Prevalence of PLM and restless legs in a normal population

In order to evaluate the prevalence of PLM and restless legs (RLS) in a normal population we screened the files of 2200 patients evaluated in our sleep lab between 1999 and August 2003 for sleep disordered breathing. Patients with evidence of a serious medical or psychiatric disorder, patients with a history of drug abuse or dependency, including alcohol, patients requiring psychoactive medication or any other drug that might interfere with the goals of a control group were excluded. Minimal criteria for RLS as defined by the International Classification of Sleep Disorders[19] were: a) a complaint of unpleasant sensation in the legs at night; b) Disagreeable sensations of “creeping” inside the calves, often associated with general aches and pains in the legs; c) the discomfort is relieved by movement of the limbs. Patients were assessed if any form of PLM (mild, moderate or severe) appeared to be present. In this period 124 asymptomatic primary snorers (no subjective sleep complaints and a AHI <5) were identified. Finally, 102 patients between 30-50 years of age (mean age 43 ± 7 y; BMI 26 ± 4) were studied. Notably, due to financial considerations it was not possible to evaluate sleep in a series of completely normal, asymptomatic and non-snoring subjects.

Lung function tests

Lung function measurements included forced expiratory volume in one second (FEV_1), inspiratory vital capacity (IVC) and the diffusing capacity for carbon monoxide (DLCO)

by the single-breath method (Masterlab; Jaeger, Wurzburg, Germany).[20] Inspiratory and expiratory muscle strength were assessed by measuring maximal respiratory mouth pressures using the method of Black and Hyatt.[21] Maximal inspiratory mouth pressure (PiMax) was measured at residual volume (RV), whilst maximal expiratory mouth pressure (PeMax) was measured at total lung capacity (TLC) (MP 45-30; Validyne Engineering Corp., Northridge, CA, USA).

Table 5.1 Patient characteristics of the sarcoidosis population

	Overall	Group I	Group II	Group III
Number	46	19 (41%)	20 (44%)	7 (15%)
Age, years (SD:range)	45 (11:28-66)	40 (7: 28-52)	50 (13:28-66)*	42 (9:28-51)
Sex: male/female	26 / 20	10 / 9	12 / 8	4 / 3
BMI; kg/m2	29 (6)	27 (6)	32 (5)*	27 (5)+
Chest X-ray				
Stage 0	8 (17%)	3 (16%)	4 (20%)	1 (14%)
Stage I	5 (11%)	2 (10%)	3 (15%)	0 (0%)
Stage II	12 (26%)	4 (21%)	5 (25%)	3 (43%)
Stage III	17 (37%)	7 (37%)	7 (35%)	3 (43%)
Stage IV	4 (9%)	3 (16%)	1 (5%)	0 (0%)
Laboratory				
sACE U/l (9-25)"	21.8 (7.8)	19.4 (7.3)	22.8 (10.0)	23.9 (7.3)
C-reactive protein mg/l (2-9) "	14.7 (13.1)	16.9 (18.9)	14.8 (13.7)	4.0 (5.4)
Calcium mmol/l (2.10-2.60) "	2.40 (0.09)	2.41 (0.07)	2.40 (0.07)	2.37 (0.09)
Lung function				
PaCO2 kPa	5.3 (0.5)	5.3 (0.3)	5.3 (0.5)	5.3 (0.6)
PaO2 kPa	10.6 (2.0)	11.1 (1.7)	9.6 (2.3)	11.2 (1.3)
FEV1 % Pred	82 (20)	78 (24)	85 (15)	86 (23)
Kco % Pred	82 (18)	83 (21)	82 (19)	82 (11)
PiMax; cm H2O	-84 (30)	-85 (35)	-77 (24)	-107 (17)
PeMax; cm H2O	89 (32)	79 (27)	90 (34)	119 (20)*

Group I cases without OSA and without PLM; Group II cases with OSA with or without PLM; and Group III cases with PLM only. Data are expressed as mean with standard deviation (SD) in parentheses. If appropriate a range or percentage of the total number is given. BMI = body mass index; FEV_1 = forced expiratory volume in one second; KCO = transfer coefficient of the lung for CO; PiMax = maximal inspiratory muscle pressure; PeMax = maximal expiratory muscle pressure; PLM = periodic leg movements; sACE = serum angiotensin converting enzyme.

" Reference ranges of laboratory values in parentheses; *$p < 0.05$ compared with Group I; $^{+}$ $p < 0.05$ compared with Group II, Mann-Whitney U-test.

Polysomnography

Polysomnography during the night was performed, using EEG, EOG and EMG measurements (Brainlab^{R}, OSG, Reet, Belgium). Sleep stages were scored according to the classic Rechtschaffen and Kales criteria.[22] This allowed determination of total sleep time (TST) defined as the total sleep period minus periods awake during this period, sleep efficiency index (SEI) defined as the ratio of TST/SPT, sleep latency (SL)

and relative duration of sleep stages all expressed as percentage of sleep period time (SPT). Ribcage and abdominal movements were monitored with respiratory inductance plethysmography (Respitrace^{R}; Ambulatory Monitoring, Ardsley, NY), which uses two transducers wrapped around the rib cage and abdomen.[23,24] The sum of these two movements represents the flow. This device also allows differentiation of obstructive from central apnoeas on the basis of out of phase movement of the ribcage and abdominal components from the Respitrace signal.

Analysis for upper airway resistance syndrome was not performed, since no Respitrace software was available. Central and obstructive apnoeas and hypopnoea were defined according to classic criteria.[19] Central sleep apnoea was only considered when visibly detectable deflections in flow and thoracic and abdominal movements were completely absent. Hypopnoea was defined as a reduction in airflow with at least 50% and a 4% drop in oxygen saturation. Oxygen saturation (SaO_2) was measured by pulse oximetry. Microarousals were scored according to criteria of the American Sleep Disorders Association (ASDA).[25] A computer analysis was performed into the origin of the arousals (from leg movement or respiratory events). A respiratory arousal index was calculated based on the number of respiratory arousals per hour of sleep, occurring within a range of (-5 s to +5 s) of end of the respiratory event.

Leg movements

Leg activity was recorded from both anterior tibialis muscles as described by Coleman.[26] Leg movements were scored using Coleman's criteria.[26] Movements during awakenings or wakefulness were not taken into consideration and only those movements occurring after a minimum of 10 s of continuous sleep were accepted as part of a PLM episode. Movements were scored irrespective of whether they occurred in one or both legs.

PLMS were scored in any stage of sleep when the following criteria were fulfilled: 1) The movements occurred as part of a series of four separate movements that were separated by at least 5 but no more than 90 s. 2) The duration of the movements was between 0.5 and 5 s. 3) An end of PLM episode was caused by a greater than 90-s interval without movements.

All movements were evaluated for the presence or absence of an accompanying arousal[27], defined as a change in EEG pattern to alpha waves, within 5 s before or after the start of leg EMG activity. Leg movements occurring simultaneously with or immediately after a respiratory event (apnoea or hypopnoea) were also scored. The following variables were derived: 1) LMI (Leg Movement Index: total number of leg movements per hour of sleep), overall and during NREM and REM sleep. 2) PLMI (Periodic Leg Movement Index: number of periodic leg movements per hour of sleep), overall and during NREM and REM sleep. 3) LMAI (Leg Movement Arousal Index: the number of leg movements leading to an EEG arousal per hour of sleep). 4) PLMAI

(Periodic Leg Movement Arousal Index: the number of periodic leg movements leading to an EEG arousal (>3 s) per hour of sleep). 5) The number of PLM sequences of at least 4 periodic leg movements. 6) Moreover, total duration of PLM (the cumulative duration of all PLM-sequences), the average length of a PLM sequence, the average length of one single periodic leg movement and the mean PLM-interval (mean interval between two periodic leg movements) were evaluated. A PLMI greater than 5 is considered pathological.

Study design

Patients were only evaluated once with full polysomnography (Dept of Respiratory Medicine, University Hospital Maastricht). Criterion for obstructive sleep apnoea (OSA) was an apnoea hypopnoea index (AHI) >5, while criterion for a periodic leg movement disorder was a periodic leg movement index (PLMI) >5. Patients were divided into three groups: Group I: AHI <5 and PLMI <5 (no OSA, no PLM), Group II: AHI >5 (OSA, with or without PLM) and Group III: AHI <5 and PLMI >5 (only PLM).

Analysis of data

The parameters obtained from each patient were analysed statistically using Kruskal-Wallis ANOVA and Mann-Whitney U-test (post-hoc analysis). All analyses were performed using the CSS Statistica^{R} package from Statsoft, USA. Spearman correlation analysis was also performed.

Results

Patient characteristics are shown in table 5.1. In 19 patients (41%) no OSA or PLM was present (Group I). In 20 (44%) of the cases OSA was demonstrated [(60% with PLM (n=12), 40% without (n=8), Group II]. Group II consisted of 12 males and 8 females and PLM occurred in 7/12 (58%) of the males and in 5/8 (62%) of the females. Six of the eight female OSA patients (75%) were postmenopausal (≥50 years old). In 7 patients (15%) significant PLM without OSA was found [Group III; 4/26 (15%) of the males and 3/20 (15%) of the females]. This means that 42% (11/26) of our male sarcoidosis patients and 40% (8/20) of our female sarcoidosis patients demonstrated a primary or secondary form of PLM.

Based on our clinical sleep questionnaire 52% of the studied patients reported the presence of restless legs syndrome (RLS)(46% of men and 60% of women). The prevalence of RLS in the subgroups was 47% (9/19) in Group I (40% in men, 56% in women), 45% (9/20) in Group II (42% in men, 63% in women) and 71% (5/7) in Group III (75% in men, 67% in women). In our healthy control group the overall prevalence of

PLM was 13.7% (14/102). In male patients the PLM prevalence was 17.8% (13/73), while in female patients it appeared to be only 3.4% (1/29). To date, RLS were reported less frequently by 1.4% (1/73) of the control men and in 6.9% (2/29) of the control women. The lowest transfer coefficient of the lungs (KCO) was 59% predicted.
Oral corticosteroids were used by 21% (4/19) (Group I), 45% (9/20) (Group II) and 28% (2/7) (Group III) of the patients at the time of the polysomnography. In tables 5.2 and 5.3 the results of the breathing pattern and sleep structure are summarized, respectively.
Group II had, due to the definition, a significantly higher respiratory disturbance compared with Group I and Group III. This was also reflected in some of the oxygen saturation parameters. In Group II men and women showed comparable respiratory disturbance (AHI 20 ± 18 vs. 17 ± 11, p=0.67), while women were more obese (BMI 30 ± 4 vs. 35 ± 5, p=0.02).
No differences in sleep quality and in distribution of sleep stages (REM-latency and delta-latency) could be found *(*table 5.3*).* Subanalysis of sleep characteristics according to sex in Group II showed more Stage 4 sleep in females suffering from OSA compared with males with OSA (8 ± 5 vs. 3 ± 1, p=0.02).

Table 5.2 Nocturnal breathing pattern of the sarcoidosis population studied: Group I cases without OSA and without PLM; Group II cases with OSA with or without PLM; and Group III cases with PLM only

	Group I	Group II	Group III
OAI; n/h	0 (0)	3 (4)*	0 (0)$^{+}$
CAI; n/h	0 (0)	2 (3)*	0 (0)$^{+}$
HI; n/h	1 (1)	14 (13)*	1 (1)$^{+}$
AHI; n/h	1 (1)	19 (16)*	1 ± 1^{+}
SaO_2 <90%; %TIB	16 (28)	24 (20)	8 (7)
SaO_2 Min; %	82 (11)	80 (6)	86 (5)$^{+}$
Time SaO_2<88%; min	17 (48)	15 (22)*	1 (2)$^{+}$
Mean SaO_2; %	92 (3)	92 (2)	93 (2)

Data are expressed as mean with standard deviation (SD) in parentheses.
PLM= periodic leg movements; OAI= obstructive apnoea index; CAI= central apnoea index; HI= hypopnoea index; AHI= apnoea hypopnoea index; SaO_2 Min= minimal oxygen saturation; n/h= number an hour; * p< 0.05 compared with Group I; + p<0.05 compared with Group II, Mann-Whitney U-test.

Distribution of the AHI according to gender showed a male/female ratio of 6/5 for AHI 5-15, 4/2 for AHI 15-30 and 2/1 for AHI >30, respectively. The two premenopausal women showed only mild OSA (10 ± 1). In 6 male OSA and in 3 female OSA patients CPAP therapy was indicated (AHI ≥15, CPAP criterion for the Netherlands). Sleep fragmentation (arousal index) was comparable in all groups. High LMI was present in all groups (LMI >5), which was periodic in 46.7% (Group II) and in 81.7% (Group III), respectively *(*table 5.4*).* Statistically higher values for LMI and PLMI (by definition) were found in Groups II and III, with the highest PLMI found in Group III (p<0.01). An

evaluation of the distribution of (periodic) leg movements showed relatively higher indices throughout NREM/REM sleep (LMI-NREM, LMI-REM, PLMI-NREM, PLMI-REM), compared with the indices based on total sleep time (TST), in all groups. There was only a (non-significant) trend towards higher PLMI/LMI in NREM. LMI-NREM appeared to be significantly higher than LMI-REM in Group II only (p=0.03). PLMI-NREM was significantly higher in Group III compared with Group II, while PLMI-REM was unchanged. No sex differences were found. The arousal indices for (periodic) leg movements (LMAI, PLMAI) were small, but substantially contributed to overall arousal index (table *5.5*) in Group II [PLMAI 31% of arousal index, LMAI 46% of total arousal index, Respiratory arousal index 31% of arousal index] as well as in Group III [PLMAI 8% of arousal index, LMAI 50% of total arousal index, Respiratory arousal index 8% of arousal index], thus explaining 33% (in Group I), 77% (in Group II) and 58% (in Group III) of all detected arousals. In Group III female patients tended to have a higher arousal index (19 ± 11 vs. 9 ± 7, p=0.24), higher LMAI (13 ± 9 vs. 4 ± 3, p=0.14) and higher PLMAI (10 ± 8 vs. 4 ± 3, p=0.30), but without statistical significance. Nonparametric Spearman correlation analysis in the whole group showed only a weak correlation between LMI and AHI (r=0.30, p=0.03), while no correlations were found with daytime or nocturnal oxygen parameters.

Daytime SaO2 correlated only with SaO2 <90% (r=-0.44, p=0.03). No other daytime parameters correlated with the level of nocturnal hypoxaemia, not even KCO, PiMax or PeMax. Correlation analysis between leg parameters and nocturnal sleep parameters showed a significant positive correlation between leg movement interval and arousal index (r=0.38, p<0.01). No correlation was found between leg parameters and REM sleep latency or slow wave sleep latency.

Table 5.3 Sleep characteristics of the sarcoidosis population studied: Group I cases without OSA and without PLM; Group II cases with OSA with or without PLM; and Group III cases with PLM only

	Group I	**Group II**	**Group III**
TST; min	405 (100)	371 (93)	383 (91)
SEI; %TST/SPT	83 (11)	76 (13)	83 (12)
REM; %SPT	16 (4)	12 (7)	15 (4)
REM-SL; min	111 (58)	119 (93)	96 (34)
Delta-SL; min	27 (28)	53 (74)	28 (18)
Stage 1; %SPT	8.1 (4.1)	10.2 (7.6)	6.5 (4.0)
Stage 2; %SPT	41.6 (11.9)	40.2 (15.8)	46.0 (11.4)
Stage 3; %SPT	9.9 (6.6)	8.3 (7.7)	12.3 (7.8)
Stage 4; %SPT	7.9 (6.6)	5.2 (4.8)	3.6 (5.0)
Delta; %SPT	18 (10)	13 (11)	16 (9)
Arousal Index	10 (6)	13 (15)	12 (9)

Data are expressed as mean with standard deviation (SD) in parentheses.
PLM= periodic leg movements; TST= total sleep time; SEI= sleep efficiency index; SPT= sleep period time; SL= sleep latency; REM= rapid eye movement sleep; Stage 1 and 2: light sleep; Stage 3 and 4: deep sleep (Delta). ;* p< 0.05 compared with Group I; + p<0.05 compared with Group II, Mann-Whitney U-test.

Table 5.4 Presence of leg movements in the sarcoidosis population studied: Group I cases without OSA and without PLM; Group II cases with OSA with or without PLM; and Group III cases with PLM only

	Group I	Group II	Group III
All Leg Movements			
LMI; n/h	6 (4; 0-16)	21 (16; 1-61)*	52 (26; 15-206)+
LMI-NREM; n/h	6 (3; 1-14)	21 (18; 1-74)*	50 (72; 17-212)+
LMI-REM; n/h	11 (10; 0-34)	11 (9; 0-33)	56 (70; 6-175)
LMAI; n/h	2 (2; 0-8)	6 (9 ; 1-42)*	6 (6; 2-6)+
Periodic Leg Movements			
PLMI; n/h	1 (2; 0-5)	10 (13; 0-45)*	30 (32; 7-98)*+
PLMI-NREM; n/h	2 (3; 0-14)	16 (22; 0-88)*	47 (73; 8-210)*+
PLMI-REM; n/h	1 (3; 0-12)	8 (28; 0-126)	33 (67; 0-180)
PLMAI; n/h	1 (1 ; 0-2)	4 (8; 0-28)*	6 (5; 1-16)+
PLM-sequences ; n	1 (2 ; 0-6)	7 (7 ; 0-24)*	15 (7 ; 8-25)*+
Total duration of PLM (min)	5 (6; 0-20)	32 (36; 0-126)*	77 (56; 32-194)*+
Mean length PLM series (s)	122 (143; 0-486)	191 (143; 0-527)*	359 (134; 193-521)*+
Mean duration one PLM (s)	1.5 (1,4; 0-4,3)	1.5 (0,9; 0-3,1)	1.9 (0,4; 1,4-2,7)
PLM-interval (s)	25 (25; 0-80)	30 (17; 0-52)	35 (11; 17-49)

Data are expressed as mean with standard deviation (SD) and range in parentheses.
LMI= total number of leg movements per hour of sleep; LMAI= the number of leg movements leading to an EEG arousal per hour of sleep; PLMI= periodic leg movement PER OUR OF SLEEP; nrem= nin raoid eye movement sleep; rem- rapid eye movement sleep;PLMAI= the number of periodic leg movements leading to an EEG arousal per hour of sleep; n/h= number an hour; total duration of PLM: cumulative duration of all PLM-sequences; PLM-interval: mean interval between two periodic leg movements.* p< 0.05 compared with Group I; + p<0.05 compared with Group II, Mann-Whitney U-test.

Discussion

In this study OSA was frequently found, while PLM and restless legs were also common. Surprisingly, in all groups the LMI was high. Arousal indices were found to be high in all groups. The high number of arousals did not influence the sleep efficiency index (SEI) in our patients. However, SEI is mainly a parameter for the macrostructure of sleep, rather than expressing the microstructure of sleep. Our studied sarcoidosis patients reported the presence of RLS very often (approximately 50%) compared with our snoring control group and also compared with prevalence rates reported by others. Saletu et al. reported a prevalence of 22% in women vs. 12% in men among 1000 Austrians of all age groups.[28] Ohayon et al. reported an even lower prevalence of restless legs of 4.1% in a general population study in the age range 30-50 years old.[29] This latter observation was more or less in accordance with our observation in our used control group.

The reported prevalence of PLM in a general population of the same age range is 3.7%, which is much lower than the prevalence we found in our patients.[29] The latter authors also reported that the odds ratio for loud snoring to get PLM was 1.06, supporting our

choice for heavy snorers as healthy controls. Some authors reported limited contribution of PLM to the arousal indices (low PLMAI between 19% and 42% of PLMI)[30-33], but most studies do not define the interval between PLM and arousal. In PLM we also found that PLMAI was 20% of PLMI. Only Eisensehr et al.[31] found higher rates (42%). When we looked at OSA patients in Group II, however, also high rates (40%) were found. The LMAI could even explain 50% of arousals in OSA as well as in PLM.

Although the presence of OSA in patients with interstitial lung disease is rare[34], we found OSA highly prevalent in sarcoidosis, as was also reported by others recently.[10] The high prevalence of RLS and (periodic) leg movements in (male and female) sarcoidosis patients is a new finding, which is not yet described or explained up to the present. Recently, Hoitsma et al.[15,35] described the presence of small fiber neuropathy in sarcoidosis, based on temperature threshold testing and a decreased density of intra-epidermal nerve fiber. Moreover, Polydefkis et al. reported an association between small fiber neuropathy and restless legs syndrome.[18] We also found high rates for restless legs in our study population, which was even more pronounced than for PLM. Whether the presence of small fiber neuropathy contributes to the development of RLS and/or PLM in sarcoidosis has to be explored.

Several other reasons may explain the development of OSA and PLM in sarcoidosis, like pronounced muscle involvement and infiltration of the upper airway by sarcoidosis before treatment with corticosteroids.[12] Moreover, myopathy as well as an increase of fat deposition in the neck and upper part of the body are well-known side-effects of corticosteroids[36] and could justify the high prevalence of the disorder in a relatively young female population. Sarcoidosis patients with OSA also demonstrated the highest body mass index. So, weight gain together with myopathy involving the pharyngeal musculature could contribute to the development of sleep apnoea. An argument against muscle weakness to explain the presence of OSA is the relatively preserved PiMax and PeMax in this study. Moreover upper airway strength in OSA has been shown to be preserved or even increased, as was shown for the genioglossus and tensor palatini muscle.[37,38] The number of patients treated with corticosteroids was also comparable in all groups, arguing against an important influence of drug treatment. The intake of corticosteroids can however influence the levels of catecholamines, leading to motor excitation and increase in (P)LM.

Myopathy involving the peripheral musculature could also contribute to the development of PLM. Asymptomatic granulomatous muscle involvement in sarcoidosis has been reported with a prevalence of 80%, whereas symptomatic muscle involvement is much less common (1.4-2.3%).[36] The symptomatic involvement that has been described varies from a palpable nodular type to an acute myositis, and chronic myopathy type. Usually, patients present with pain, weakness, fatigue, muscle atrophy including respiratory muscles and sometimes fever. Recently, Wirnsberger et al. demonstrated

reduced respiratory muscle strength and endurance time in sarcoidosis patients with normal lung function.[39] Moreover, the respiratory muscle function seemed to quantify and characterize the functional impairment in patients with sarcoidosis and reflected symptoms, such as fatigue and general weakness.[39] We found however relatively preserved PiMax and PeMax in this study, which may also argue against myopathy to explain the presence of PLM. No arguments could be found to explain the presence of PLM due to the appearance of nocturnal hypoxaemia, as shown in patients with COPD.[40,41] The highest degree of hypoxaemia was found in both group I and group II. Subanalysis of OSA patients with or without PLM did also not show any difference in the oxygen desaturation time. No difference in CO_2 level was found and could thus not be used to explain differences in PLM activity.

Table 5.5 Arousal indices related to leg movements and respiratory events in the sarcoidosis population studied: Group I cases without OSA and without PLM; Group II cases with OSA with or without PLM; and Group III cases with PLM only

	Group I	Group II	Group III
Arousal Index; n/h	10 (6; 0-21)	13 (15; 0-73)	12 (9; 1-27)
Leg Movement Arousal Index; n/h	2 (2; 0-8)	6 (9; 1-42)*	6 (6; 1-20)*
Respiratory Arousal Index; n/h	1 (1; 0-1)	4 (9; 0-36)*	1 (1; 0-1)+

Data are expressed as mean with standard deviation (SD) in parentheses.
* $p < 0.05$ compared with Group I, Mann-Whitney U-test; + $p < 0.05$ compared with Group II, Mann-Whitney U-test.

The influence of sleep stages on (P)LM distribution was also less pronounced in sarcoidosis. Previous studies have demonstrated that PLM were found to be most frequent during NREM sleep and almost absent during REM-sleep.[42,43] The presence of a significant number of (P)LM during REM sleep suggests that REM sleep suppression of spinal motoneurons is not complete throughout the REM sleep period in sarcoidosis patients. Notably, leg movements during wakefulness were not scored due to the Coleman criteria. Moreover, there is confusion about the criteria to be used to identify (periodic) leg movements during wakefulness.

The high prevalence of OSA in our female patients might be explained by the slightly higher disease rate of sarcoidosis for women. In the only population based incidence study of sarcoidosis in the United States, rates were 5.9 per 100,000 personyears for men and 6.3 per 100,000 person-years for women [44], which results in a male/female ratio of 0.9/1. In the ACCESS study 34% male and 66% female sarcoidosis patients were included.[45,46] Based on a questionnaire study among the members of the Dutch Sarcoidosis Society 37% are men and 63% are female (n=1026, age 47 (12) y)[47], confirming the ACCESS data from the USA**.** The ratio of men to women with OSA (without sarcoidosis) in clinical and community studies appeared to be considerably higher (approximately 5 to 8/1 and 2 to 3/1, respectively). Increased complaints of

insomnia, fatigue, headache, and dissatisfaction with life could lead primary care and specialist physicians to under or mis-diagnose OSA in women.[48] We found that female OSA patients were more obese than male OSA patients. However post-menopausal women with OSA (n=6) and age-matched male OSA (n=7) had approximately equivalent body mass indices (32 (4) and 36 (5) respectively, p=0.19), paralleling observations in OSA without sarcoidosis.

When clinically relevant OSA is present, CPAP application can be considered, since this device is the golden standard for OSA treatment. In patients demonstrating a decrease of PLM during CPAP therapy, movements could be considered as a consequence of OSA. Starting CPAP has to be performed carefully, since PLM can be unmasked during CPAP therapy, causing persistent complaints of diurnal symptoms.[49] This has to be studied in detail in the sarcoidosis population. In our series 9 patients used chronic CPAP therapy, but follow-up polysomnographies were not yet performed. The most suitable drug treatment for PLM is also not yet determined. Since pain is sometimes involved in the presence of PLM or neuropathy, it is possible that PLM in sarcoidosis is most adequately treated with drugs as gabapentine, whereas clonazepam or dopamine agonists are other possibilities. This needs further evaluation.

Sleep disorders are a substantial problem in chronic sarcoidosis. To date, the greatest impact on quality of life in sarcoidosis, as seen in the clinical practice, seems to be caused by symptoms such as fatigue and sleep disorders. Drent et al. evaluated health status and quality of life of sarcoidosis patients with the Sickness Impact Profile and found high scores for the item Sleep and Rest[8] compared with a control group and compared with sarcoidosis patients without complaints. Sleeping problems appeared to be associated most with the Beck Depression Inventory and the Cognitive Depression Index, those with sleeping problems being more depressed (r=0.63).[8] With the WHOQOL-100 an association between fatigue and physical health (facet sleep and rest) was also demonstrated, but not with depression (although lower scores were found in sarcoidosis)[9] It was concluded that sarcoidosis patients developed depressive symptoms as an expression of exhaustion by the disease. Although a normal REM-sleep latency was present in the present series, this does not exclude the existence of a depressed mood state in these patients[50,51] Possibly, an improvement in the experienced stress level can be obtained with CPAP, decreasing sympathetic activity.[52]

Direct measurement of the sleep and breathing pattern by polysomnography seems necessary to assess sleep and fatigue objectively and to evaluate whether intervention strategies in this group of patients are of benefit (CPAP, drugs, cognitive behavioural therapy), since neither the FEV_1, nor the sACE level in patients suffering from sarcoidosis accounted for a significant variation in the AHI or PLMI. Moreover, no relation with radiographic stage or respiratory muscle strength was found. Also, no correlation between daytime PaO_2 and nocturnal hypoxaemia (time <88%) was demonstrated.

Therefore, overnight monitoring of gas exchange needs to be considered in patients with fatigue, even in the absence of clinical suspicion of OSA.

Although sleep disorders appeared to be a substantial problem in chronic sarcoidosis, the contribution of PLM to fatigue and sleepiness is controversial.

A recent study found that arousals recorded with PLM more often precede rather than follow the movements.[30] These authors however used an interval of 10 s before or after PLM, what seems too long an interval to us. Therefore we preferred to use an interval of 5 s. Shorter intervals have the disadvantage that an event-arousal relationship can be underestimated. Chervin et al. concluded that incidental PLM during sleep are not associated with excessive daytime sleepiness in a clinical series of 1124 adult patients.[53] Montplaisir et al. concluded that the validity of PLM disorders as a distinct entity is highly questionable, since PLM are not more prevalent in patients with insomnia or hypersomnia than in control subjects.[54] Mendelson et al. found no relationship between PLMAI and reporting subjective bad sleep.[55] In contrast, other authors have found a relationship between PLM and sleepiness.[56] In the present study an important number of arousals could be explained by OSA and PLM (77% and 58% in each group). However, this relationship was not found when using a shorter interval (2 s). Moreover, as many studies do not report the event-arousal interval duration comparisons are impossible. Therefore, a firm conclusion about a causal relationship between PLM and non-restorative sleep is not yet possible. Other arousal disorders could also be involved, like an upper airway resistance syndrome (UARS), by pharyngeal infiltration of the upper airway by sarcoidosis, leading to flow limitation.[57] Pharyngoesophageal pressure measurements have to be performed to prove this hypothesis.[58] It has also been shown that PLM are associated with autonomic (subcortical) arousals, which can lead to tachycardia, rises in blood pressure, vasoconstriction and decreased peripheral pulses.[59,60] These types of arousal can lead to daytime sleepiness too. However, these types of arousals have not been evaluated in this study. The likelihood of UARS is less clear, since only 42% (Group I) and 57% (Group III) of the patients reported snoring. Another reason for arousals could be the presence of pain stimuli during sleep, resulting in EEG arousal responses. Recently it was reported that many sarcoidosis patients have pain complaints (72% of the 821 studied patients, mostly arthralgia and muscle pain), which may also play a role in movements and/or arousals.[61]

Although this study contains an interesting message, it also has some limitations. Firstly, we used a low cut-off point for the selection of PLM patients (PLMI >5). It should be questioned whether this criterion is abnormal, since it has been chosen arbitrarily (historically), without documented clinical correlation. Secondly, we also did not measure the multiple sleep latency test (MSLT), to evaluate daytime sleepiness. Third, autonomic arousals measurements were not performed. Fourth, we have not taken into account whether arousals recorded with PLM more often precede rather than follow the

movements, as was reported by Karadeniz[30] (based on a 10 s interval). Fifth, although we used a Respitrace signal for monitoring ventilation, an analysis for upper airway resistance syndrome was not performed, since no software for automatic analysis of small phase angle changes was available. It was however shown that respiratory inductance plethysmography is the least sensitive non-invasive indicator of flow limitation.[62] Last but not least, it has to be underlined that high arousal indices can occur in normal subjects when evaluated by a 1-night polysomnography.[63] This latter could indicate that the technical equipment could influence the arousal pattern or that high arousal indices are not linked with daytime sleepiness.

Conclusions

RLS, OSA and PLM frequently occur in sarcoidosis patients suffering from awakening unrefreshed in the morning. The exact extent of the presence of RLS, OSA and PLM to the complaints of sarcoidosis patients remains still controversial, however. Application of CPAP therapy in OSA is self-evident, while the most suitable drug treatment for PLM has not yet been studied. Further studies, also including asymptomatic sarcoidosis, should focus on the presence of RLS, PLM and OSA in relation to fatigue in sarcoidosis. Also studies assessing intervention strategies are needed to evaluate the impact of these disturbances.

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