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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Disorders of sleep in spinal and bulbar muscular atrophy (Kennedy's disease)

Lisa Langenbruch[1] · Salvador Perez-Mengual[1] · Christian Glatz[1] · Peter Young[2] · Matthias Boentert[1,3]

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Abstract

Introduction Spinal and bulbar muscular atrophy (SBMA) is a progressive, X-linked lower motor neuron disorder exclusively affecting men. Since knowledge on sleep disorders in SBMA is scarce compared to other motoneuron diseases, this retrospective case-control study aimed to investigate sleep and sleep-related breathing in patients with SBMA.

Methods In 23 non-ventilated patients with SBMA (median age 52 years), clinical disease characteristics, forced vital capacity and diagnostic polysomnographies were retrospectively evaluated. In 16 patients, overnight transcutaneous capnometry was available. Twenty-three male control subjects with chronic insomnia were matched for age and body mass index.

Results In patients with SBMA obstructive sleep apnoea (OSA, apnoea-hypopnoea index/AHI > 5/h) was more frequent than in control subjects (14/23 or 61% vs. 6/23 or 26%, $p = 0.02$), and median AHI was significantly higher in patients (9.0/h vs. 3.4/h, $p < 0.01$). Among SBMA patients, the AHI was not related to age or body mass index. Alveolar hypoventilation as reflected by nocturnal hypercapnia was found in 3/16 patients. Rapid eye movement (REM) sleep without atonia was present in 44% of SBMA patients but only in 4% of controls ($p < 0.01$). During REM and non-REM sleep, no behavioural abnormalities were observed in either group. Periodic limb movements in sleep (index > 15/h) were frequent in SBMA patients but rarely disrupted sleep.

Conclusions In patients with SBMA, sleep-disordered breathing may comprise both OSA and nocturnal hypoventilation. REM sleep without atonia may also be found, but its clinical significance remains unclear. In patients complaining of sleep-related symptoms, cardiorespiratory polysomnography and transcutaneous capnometry are recommended.

Keywords Spinal and bulbar muscular atrophy · Kennedy's disease · Sleep-disordered breathing · Alveolar hypoventilation · REM sleep · REM sleep behavioural disorder

Introduction

Spinal and bulbar muscular atrophy (SBMA, syn.: Kennedy's disease) is a multi-system disorder which is caused by a CAG trinucleotide expansion in the androgen receptor gene on chromosome X [17]. Due to the hemizygous mechanism of inheritance, SBMA fully manifests only in men. Endocrine symptoms comprise gynecomastia and reduced fertility due to partial androgen insensitivity. From the fourth to fifth decade, patients show signs of lower motor neuron dysfunction including fasciculations and atrophy of facial and neck muscles, bulbar muscle weakness leading to dysphagia and dysarthria, and hand tremor [2]. With disease progression, proximal weakness of arms and legs may occur. Recurring laryngospasms have been reported in nearly 50% of patients [23]. Distal-symmetric sensory neuropathy, impaired glucose tolerance, elevated liver enzymes and dyslipidaemia may also be present [2]. The time of symptom onset is closely linked to the number of CAG repeats in the androgen receptor gene but overall neurological disability and the rate of disease progression are not [2, 15]. Women carrying one or two affected X chromosomes will not develop SBMA but may present with frequent muscle cramps or show mild chronic neurogenic

✉ Matthias Boentert
matthias.boentert@ukmuenster.de

[1] Department of Neurology with Institute of Translational Neurology, University Hospital Münster (UKM), Albert-Schweitzer-Campus 1, A1, 48149 Münster, Germany

[2] Department of Neurology, Medical Park Bad Feilnbach, Bad Feilnbach, Germany

[3] Department of Medicine, UKM Marienhospital Steinfurt, Steinfurt, Germany

changes on needle electromyography [19]. SBMA is a motor neuron disorder, making it a differential diagnosis of bulbar onset amyotrophic lateral sclerosis (ALS) in male patients [4].

Whereas sleep and, in particular, sleep-disordered breathing has extensively been studied in ALS, little is known about sleep disorders in patients with SBMA. One case-control study including 9 patients found obstructive sleep apnoea (OSA) in 6 patients, rapid eye movement (REM) sleep without atonia in 3 individuals and periodic limb movements in sleep in 2 patients [22]. This small study did not apply transcutaneous capnography, which detects sleep-related hypoventilation with much higher sensitivity than mere pulse oxymetry in patients with neuromuscular disorders [8, 14]. The present study aimed to extend the current knowledge on sleep characteristics in SBMA, with a special focus on sleep-related breathing since neurogenic weakness of pharyngeal or inspiratory muscles puts patients at risk of upper airway obstruction and nocturnal hypoventilation, respectively [7, 8]. In addition, REM-sleep-associated events were specifically evaluated.

Patients and methods

Patients

We retrospectively evaluated clinical data and polysomnography (PSG) records from 26 patients with SBMA who consecutively presented for diagnostic sleep studies to our neurological sleep laboratory between 2004 and 2017. Reasons for admission included self-reported symptoms such as sleep disturbances, non-restorative sleep or excessive daytime sleepiness. In all individuals, SBMA was genetically confirmed. Cardiorespiratory polysomnography (PSG) was performed as part of the routine clinical workup in patients with neuromuscular disorders. Three patients were excluded because of insufficient total sleep time < 2 h ($n = 1$), prior initiation of non-invasive ventilation ($n = 1$) and recently established tracheostomy-invasive ventilation following acute pneumonia ($n = 1$).

Finally, 23 non-ventilated patients were included in this case series. As control subjects, 23 male patients with primary insomnia were selected in whom full PSG had been performed. Controls were matched for age (± 3 years) and body mass index (BMI, ± 2 kg/m^2).

Sleep studies

All patients and controls underwent diagnostic PSG according to standard guidelines [6]. PSG comprised electroencephalogram, electrooculogram, surface electromyogram of the chin and tibialis anterior muscles, pulse oximetry, nasal pressure and quantitative effort registration. Sleep stages and sleep-associated events were manually scored by two blinded raters [5]. In the presence of sleep-related complaints, an apnoea-hypopnoea index (AHI) > 5/h was considered confirmative for diagnosis of sleep apnoea [5]. An obstructive apnoea was scored when nasal flow amplitude decreased by ≥ 90% for ≥ 10 s and thoraco-abdominal effort was present throughout the event. A central apnoea was scored when the flow amplitude decreased by ≥ 90% for ≥ 10 s in the absence of any respiratory effort. If the latter re-occurred during an initially central apnoea, the event was categorized as a mixed-type apnoea. Hypopnoeas were scored when the flow amplitude decreased by ≥ 30% for ≥ 10 s with a ≥ 3% reduction of the peripheral oxygen saturation compared to the pre-event baseline. Transcutaneous capnometry (Sentec, Therwil, Switzerland) was available for only 16 patients since routine clinical practice had changed in the interim. Nocturnal hypercapnia was diagnosed when transcutaneous carbon dioxide tension ($p_{tc}CO_2$) either exceeded 50 mmHg or increased from the awake supine baseline by more than 10 mmHg during sleep ($\Delta ptcCO_2$) [24]. REM sleep periods were re-examined in 18 patients and all controls since raw data for re-evaluation of REM sleep were incomplete for 5 patients. These patients were not included in REM sleep analysis regardless of the initial written report on muscle tone and behaviour during REM sleep. Surface electromyogram (EMG) was recorded from the chin and the tibialis anterior muscles according to AASM guidelines [6]. In each subject, EMG activity during REM sleep was manually evaluated and classified as tonic, phasic or "any" (either tonic or phasic). Tonic EMG activity was scored only in the mentalis muscle using 30-s epochs when increased EMG activity was present for > 50% of the total epoch with an amplitude exceeding twice the background EMG or more than 10 μV. Phasic EMG activity was evaluated in mini-epochs of 3 s each and defined as any burst of EMG activity lasting between 0.1 and 5.0 s with an amplitude of at least twice the background EMG activity [12].

The day before diagnostic sleep studies, all patients completed the Epworth Sleepiness Scale (ESS) which is a widely used 8-item questionnaire for self-assessment of sleep propensity in monotonous everyday situations [16]. The ESS yields a sum score of 0 to 24 with a cut-off of 11 or more reflecting excessive daytime sleepiness. The same day, forced vital capacity (FVC) was measured using handheld spirometry in the sitting and supine position in 12 patients.

Statistical methods

Statistical data analysis was performed using SPSS® v24.0 (IBM Inc., Armonk, NY). For non-parametric data, results are shown as median and interquartile range (25–75%), with the Mann-Whitney U test or the Kruskal-Wallis test used for group comparisons as appropriate. Categorical variables were analysed using the χ^2 test or Fisher's exact test. Spearman's correlation coefficient was used for associations between continuous variables. Strength of correlation was classified as

weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) or very strong (0.80–1.00). p values < 0.05 were considered statistically significant.

Results

Group comparison

We included 23 male patients with a median age of 52 years (range 35 to 76 years). Median BMI was 25.1 kg/m^2; four patients had a BMI of 30 kg/m^2 or higher indicating obesity. None of the patients was underweight, was wheelchair-bound or had a feeding tube in place. Prevalence of distinct symptoms of SBMA among patients is depicted in Table 1. Comorbidities included sensory neuropathy (n = 8), arterial hypertension (n = 7), diabetes mellitus (n = 5), stable major depression (n = 2) and chronic obstructive lung disease (COLD, n = 2). The latter two patients were not receiving oxygen therapy. Control subjects reported arterial hypertension (n = 5), mild sensory neuropathy (n = 4), major depression (n = 4), mild COLD (n = 2, no oxygen therapy), asthma (n = 3), stable coronary artery disease (n = 2), diabetes mellitus (n = 2) and hyperthyroidism (n = 2). Both age and BMI did not differ between groups.

No patient or control subject used continuous positive airway pressure or non-invasive ventilation. Among SBMA patients, the median ESS score was 8.0, while seven patients (30.4%) reached an ESS score > 10/24 indicating excessive daytime sleepiness.

On diagnostic sleep studies, significant differences between SBMA patients and controls could be observed with regard to AHI, oxygen desaturation index (ODI), percentage of N3 sleep stage, and periodic limb movements in sleep (PLM) (Table 2). In patients with SBMA, the median AHI was 9.0/h. Obstructive sleep apnoea as defined by an AHI > 5/h was diagnosed in 14 patients (60.9%) and 6 control subjects (26.1%, p = 0.02). In nine patients (39.1%) and six controls (26.1%), the AHI ranged between 5/h and 15/h indicating mild sleep apnoea, and an AHI of 15–30/h was found in three SBMA patients (13.0%) but in none of the controls. Severe OSA (AHI > 30/h) was present in two SBMA patients only. Two patients with predominant OSA showed a central apnoea index > 5/h.

Table 1 Prevalence of distinct symptoms of SBMA in the patient cohort

	n
Facial weakness	22
Tongue atrophy and fibrillations	10
Dysphagia	19
Dysarthria	9
Fasciculations	19
Upper limb weakness	22
Upper limb atrophy	12
Lower limb weakness	22
Lower limb atrophy	7
Tremor	3
Laryngospasms	4
Dyspnoea on exertion	2
Elevated liver enzymes (> 2× upper limit)	1
Gynaecomastia	9

Patients with SBMA

Among SBMA patients, the ESS sum score and BMI were strongly correlated (r = 0.65, p < 0.01). Moderate correlation was found between the ESS sum score and oxygen desaturation time below 90% (r = 0.51, p = 0.02), whereas BMI, ESS sum score and time since symptom onset were not statistically related to AHI. Transcutaneous capnometry revealed nocturnal hypercapnia in 3/16 patients. Specifically, $\Delta ptcCO_2$ was > 10 mmHg in one patient with a baseline of 34.4 mmHg and a maximum of 48.4 mmHg, and in two patients, maximum $p_{tc}CO_2$ was 52.5 mmHg and 57.0 mmHg, respectively. Nocturnal capnometry was normal in the remaining 13/16 patients. No statistical correlation was found between the ESS sum score and $\Delta ptcCO_2$ or maximum $ptcCO_2$. Furthermore, time from symptom onset did not correlate with capnometry results.

Evaluation of FVC in the sitting and supine position showed a positional drop of more than 25% of the predicted value in 3/12 patients suggesting diaphragm weakness [13]. Upright FVC was normal in these subjects, but lower than 70% of the predicted value in four more patients [21].

PLM with a PLM index (PLMI) > 15/h were present in 10/23 patients (43%), and the median PLMI was 9.4/h. Median PLMI in controls was 0.1 (p = 0.049). Periodic limb movements in sleep were associated with an increased number of arousals in only 3 patients (PLM arousal index > 5/h). There was no correlation between PLMI and the ESS sum score.

REM sleep was captured and thoroughly analysed in 18 patients and 23 controls. Detailed history was not suspicious of REM sleep behavioural disorder in all study subjects. REM sleep without atonia (RSWA) was found in 8/18 SBMA patients (44.4%) and in 1/23 control subjects (4.3%, p < 0.01). Analysis of video records did not reveal any behavioural abnormalities during REM sleep in either patients or controls. Among study participants, 2/8 patients

Table 2 Demographic data and sleep parameters

	n	SBMA patients	Controls	*p*
Age (years)	23	52.0 (46–63)	52.0 (47–64)	0.88~
Time since symptom onset (years)	19	9.0 (5.0–12.0)	-	-
Time since established diagnosis (years)	22	3.0 (1.0–7.5)	-	-
BMI	23	25.1 (23.2–29.2)	25.8 (24.2–29.2)	0.45~
Forced vital capacity, FVC (% predicted)	12	71 (53–75.8)	-	-
Positional drop > 25% of FVC	12	3/12 (25%)	-	-
ESS sum score	23	8 (4–11)	6 (3–9)	0.44~
TST (min)	23	351 (313–390)	369 (326–393)	0.31#
Sleep efficiency (%)	23	77.5 (66.5–83.3)	79.1 (72.6–84.6)	0.48#
REM (% TST)	23	14.1 (12.2–18.3)	15.2 (13.0–18.2)	0.59#
N3 (% TST)	23	24.7 (16.9–30.6)	15.0 (12.4–22.0)	*0.03#*
WASO (min)	23	58 (45–82)	72 (45–115)	0.47#
AHI (/h TST)	23	9.0 (3.6–13.8)	3.4 (0.4–5.2)	*< 0.01#*
AHI > 5/h	23	14/23 (60.9%)	6/23 (26.1%)	*0.02§*
AHI > 15/h	23	5/23 (21.7%)	0/23	*0.049**
ODI (/h TST)	23	6.7 (2.1–12.4)	2.7 (0.5–4.6)	*< 0.01#*
Mean SpO_2 (%)	22	94 (93–95)	94 (93–95)	0.45#
Minimal SpO_2 (%)	22	86 (83–89)	88 (85–90)	0.12#
$t < 90\%$ (min)	22	3.7 (0.9–9.7)	2.4 (0.2–14.8)	0.7#
$t < 90\%$ (% TST)	22	1.2 (0.3–2.9)	0.6 (0–4.4)	0.58#
Baseline $ptcCO_2$	16	38.0 (36.4–40.0)	-	-
Mean $ptcCO_2$	16	39.8 (38.2–41.2)	-	-
Maximum $ptcCO_2$	16	45.1 (42.3–49.2)	-	-
$\Delta ptcCO_2$	14	6.6 (4.4–7.7)	-	-
PLMI (/h TST)	23	9.4 (2.0–50.1)	0 (0–22.7)	*0.049#*
Arousal index (/h TST)	23	9.8 (6.1–16.8)	10.4 (5.4–14.6)	0.99#
Respiratory arousal index (/h TST)	23	1.2 (0–3.5)	0.8 (0.2–1.6)	0.42#
PLM arousal index (/h TST)	23	0.4 (0–2.7)	0 (0–2.3)	0.2#
RSWA	18	8/18 (44.4%)	1/23 (4.3%)	*< 0.01**
REM behavioural abnormalities	18	0/18	0/23	-

Numbers are depicted as median and interquartile range or absolute number/percentage of individuals

SBMA, spinal and bulbar muscular atrophy; *BMI*, body mass index; *ESS*, Epworth Sleepiness Scale; *TST*, total sleep time; *REM*, rapid eye movement sleep; *N3*, slow-wave sleep; *WASO*, wake after sleep onset; *AHI*, apnoea-hypopnoea index; *ODI*, oxygen desaturation index; *SpO_2*, peripheral oxygen saturation; *$t < 90\%$*, duration of $SpO_2 < 90\%$; *CO_2*, carbon dioxide; *$ptcCO_2$*, transcutaneous carbon dioxide tension; *$\Delta ptcCO_2$*, a nocturnal increase of $ptcCO_2$ from baseline to maximum; *PLM*, periodic limb movements in sleep; *PLMI*, PLM index; *RSWA*, REM sleep without atonia; *REM*, rapid eye movement sleep

~Student's *t* test

#Mann-Whitney *U* test

§Pearson's chi-square

*Fisher's exact test

Significant *p*-values are italicized

and the control subject with RSWA reported regular intake of antidepressants but this was also true for 4/15 SBMA patients and 4/22 control subjects without RSWA. Between SBMA patients with or without RSWA no significant differences were found regarding age, total AHI, AHI in REM sleep, PLMI, arousal index, respiratory arousal index or percentage of REM sleep (data not shown).

Discussion

This study presents comprehensive PSG data and, for the first time, overnight capnography recordings from patients with SBMA. Whereas the only previous work on sleep disorders in this condition reports sleep study outcomes from only 9 affected patients, the present study is based on a larger cohort

(n = 23) [22]. It confirms that OSA prevalence appears to be substantially higher among SBMA patients than in the normal population [1]. Despite most being classified as mild sleep apnoea, five patients (21.7%) had moderate or severe OSA. In the general male population of the similar age range, OSA prevalence has been found to be 17–26% for AHI > 5/h and 7–14% for AHI > 15/h [25]. Central apnoea does not seem to be clinically relevant in SBMA, as only few central apnoeas were recorded in a small subset of patients with predominant OSA and would not have changed the clinical decision to treat with continuous positive airway pressure first (CPAP). Excessive daytime sleepiness as measured by the ESS is not related to sleep-disordered breathing in SBMA. Interestingly, age and BMI did not correlate with the AHI in patients with SBMA, suggesting that OSA is independent of two major risk factors that are known from large population-based studies [20]. This observation may be weakened by this study's small sample size but is supported by similar findings in other neuromuscular disorders [7, 8]. Pathophysiologically, weakness or decreased tone of pharyngeal muscles is likely to promote intermittent upper airway collapse during sleep.

Alveolar hypoventilation was diagnosed in three out of 16 patients in whom transcutaneous capnometry was performed. Whereas diaphragm weakness and nocturnal hypoventilation are highly prevalent in other motoneuron diseases such as ALS or spinal muscular atrophy, it has not yet been systematically described in SBMA. Only one case report refers to a patient requiring non-invasive ventilation [10]. Another study found that patients with SBMA very rarely report significant dyspnoea, resulting in relatively high scores on the respiratory items of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale [9, 11]. However, evaluation of both respiratory muscle strength and nocturnal ventilation is indispensable in SBMA patients in whom sleep-disordered breathing is suspected. In particular, diagnostic workup should include transcutaneous capnography, as sole pulse oximetry has been shown to have insufficient sensitivity for the detection of nocturnal hypoventilation in patients with neuromuscular disorders [8, 14]. It should be noted that two more patients were excluded from this case series because mechanical ventilation had already been established. Thus, the present study may even underestimate the prevalence of alveolar hypoventilation in SBMA. Detection of alveolar hypoventilation is also relevant in patients with pre-existing OSA and ongoing CPAP treatment, as these patients may need bilevel positive airway pressure therapy instead. Spirometry revealed diaphragm weakness in as many as 7/12 patients suggesting that evaluation of respiratory muscle strength may help to identify patients eligible for sleep studies and capnography.

PLMS were quite common in this study and occurred in 43% of SBMA patients which substantially exceeds the numbers previously reported [22]. However, this finding is put into perspective by the fact that corresponding arousals from sleep were rare, suggesting that the clinical relevance of PLMS is limited in this condition.

In the present study, RSWA was more frequent in SBMA patients than in the control subjects (44.4% vs. 4.3%) while REM sleep duration and AHI during REM sleep did not differ between groups. Abnormal behaviour during REM sleep was recorded in none of the 18 patients in whom full video PSG recordings were available. Moreover, detailed history was not suspicious of REM sleep behavioural disorder (RBD) in all 23 patients with SBMA. A similar percentage of SBMA patients with RSWA (33%) was reported previously, again without overt behavioural abnormalities during REM sleep [22]. With regard to other motoneuron diseases than SBMA, Lo Coco et al. found two individuals with manifest RBD and another two showing isolated RSWA in a cohort of 41 ALS patients [18]. However, evidence for RSWA and RBD in both ALS and SBMA is still scarce, and further systematic studies are needed in order to investigate whether RBD, although most frequent in α-synucleinopathies, is a pathologically distinct feature of different neurodegenerative disorders involving pathways that regulate muscle tone during REM sleep.

Limitations of this study include its retrospective design and a rather high variance of age and disease severity among SBMA patients. Furthermore, data on spirometric evaluation were lacking for 11/23 patients, and the predictive value of FVC testing for the diagnosis of nocturnal hypoventilation could not be determined. Lastly, patients with insomnia have to be considered as diseased controls, and healthy control subjects would have been preferable. This aspect is illustrated by the unsurprising fact that N3 percentage was lower in insomniac controls than in patients with SBMA [3]. However, this study aimed to evaluate sleep-disordered breathing and REM-sleep-associated events but did not specifically focus on sleep architecture.

To conclude, sleep-disordered breathing (SDB) appears to be a common finding in patients with SBMA and sleep-related symptoms. Only a small number of patients (3/23) had no evidence of sleep-disordered breathing, periodic limb movements or RSWA. Obstructive sleep apnoea is likely to be the most prevalent type of SDB, but also nocturnal hypoventilation may occur and require adequate treatment. Polysomnographic and capnometric evaluation is recommendable, and given the low predictive value of symptom questionnaires, sleep studies should be considered also in SBMA patients presenting with only mild symptoms and regardless of age or disease duration.

Authors' contributions LL analysed the data and wrote the initial draft of the manuscript. SPM and LL reviewed sleep study recordings. CG specifically analysed sleep-related breathing and behaviour during REM sleep. MB and PY designed the study, reviewed the data analyses and critically revised the manuscript. All authors have seen and approved the final version of the manuscript.

Data availability Original data were accessible to all authors. Further details can be requested from the corresponding author.

Compliance with ethical standards

Conflict of interest LL, CG and SPM declare no competing interests. PY received honoraria from UCB, Sanofi-Genzyme, VANDA, Medice, Löwenstein Medical, ResMed and Bioprojet for speaker's bureaus. He received honoraria for advisory boards from Sanofi-Genzyme and Pharnext. MB received speaker honoraria and financial research support by Sanofi-Genzyme, Löwenstein Medical and UCB (speaker honoraria only).

Ethics approval This retrospective study was based on data derived from routine clinical care and was approved by the local ethics committee. This article does not report the results of a clinical trial.

Code availability Not applicable.

Abbreviations AHI, apnoea-hypopnoea index; ALS, amyotrophic lateral sclerosis; BMI, body mass index; CO_2, carbon dioxide; COLD, chronic obstructive lung disease; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; N3, slow-wave sleep; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PLM, periodic limb movements; PLMI, periodic limb movement index; PLMS, period limb movements in sleep; PSG, polysomnography; $p_{tc}CO_2$, transcutaneous CO_2 tension; RBD, REM sleep behaviour disorder; REM, rapid eye movement sleep; RSWA, REM sleep without atonia; SBMA, spinal and bulbar muscular atrophy; SDB, sleep-disordered breathing; SMA, spinal muscular atrophy

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Comment The paper has indisputable scientific relevance and warns of the need to carefully evaluate the respiratory and sleep aspects of patients with Kennedy's disease.

Luciana Moraes Studart-Pereira

Brazil