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Original Article

Effects of long-term non-invasive ventilation on sleep structure in children with Spinal Muscular Atrophy type 2☆

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ABSTRACT

Objective: Changes of sleep architecture have been reported in children with Spinal Muscular Atrophy type 2 (SMA2), mainly represented by a decrease of arousability. No studies have evaluated the effect of long-term ventilation on sleep parameters in these children. The aim of this study was to evaluate the effects of long-term non-invasive positive pressure ventilation (LTNPPV) on sleep architecture and to assess the residual differences from normal controls.

Methods: Nine consecutive children with SMA2 underwent two distinct polysomnographic (PSG) studies, one in spontaneous breathing, and subsequently after LTNPPV. The results were then compared to 15 age-matched controls.

Results: SMA2 patients showed only slightly modified sleep architecture on LTNPPV: increased stage N2% and decreased number of awakenings, while several significant differences persisted between SMA2 patients on LTNPPV and controls (decreased total sleep time, number of awakenings, sleep efficiency, and percentage of REM sleep). Sleep microstructure, evaluated by means of the Cyclic alternating pattern (CAP) showed only marginal changes on LTNPPV (small shortening of CAP A1 subtype duration and small increase in CAP A3 index). Conversely, CAP parameters on LTNPPV showed significant differences between SMA2 patients vs. controls, with increased A1 subtype percentage and decreased percentage of A2 and A3 subtypes.

Conclusions: This is the first study in children affected by SMA2 reporting data on sleep microstructure and their changes after LTNPPV. We found persisting, small but important changes in sleep microstructure during LTNPPV in these children, suggesting that this treatment only partially improves their arousability.

1. Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem [1]. It has an estimated incidence of 1/6000 to 1/10,000 live births and a carrier frequency of 1/40 to 1/60 [2,3].

The phenotype of the disease is caused by the mutation of the SMN1 (survival motor neuron 1) gene on the long arm of chromosome 5 (homozygous deletion of exons 7 and 8), which encodes for the SMN protein. SMN2 differs from SMN1 in five nucleotide exchanges, and disease severity in SMA is inversely correlated with the number of copies of SMN2.

Patients with SMA type 1 (SMA1) have a lower number (one or two) of SMN2 copies than SMA type 2 (SMA2) patients and this characteristic explains their more severe medical condition. The clinical severity of SMA ranges from the extremely severe, prenatal onset, to the mildest adult-onset form. It is known that these

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patients develop progressive respiratory muscle weakness, which can lead to a chronic ventilatory failure, recognizable early during sleep and also during wakefulness at terminal stages. Because of their progressive respiratory failure, these patients frequently need a long-term non-invasive positive pressure ventilation (LTNPPV) during sleep.

Apnea/hypopnea index (AHI) is increased in SMA patients and sleep latency has been found to be significantly prolonged in SMA1 patients [4,5]. Furthermore, an increase in light sleep (sleep stages N1 and N2) and a decrease in slow-wave sleep (sleep stage N3), and REM sleep have been also reported [6,7].

In another study on seven children with SMA (six with SMA1, one with SMA2) with impaired sleep architecture, nocturnal non-invasive ventilation (NIV) resulted in a significant improvement in sleep architecture with higher sleep efficiency and decreased light sleep, counterbalanced by increased deep sleep, longer REM sleep, and significantly less electroencephalographic (EEG) arousals [8].

Regarding sleep microstructure parameters, analyzed by Cyclic Alternating Pattern (CAP), the SMA1 group showed a significant reduction in A2 and A3 subtypes, testifying a decreased arousability [4]. These findings have been confirmed also in children with SMA2 [7].

To the best of our knowledge, no previous studies investigated the effect of LTNPPV on the sleep microstructure in children with SMA2. Based on the above evidence, the aim of our study was to evaluate the effects of LTNPPV on sleep architecture, and microstructure (by means of CAP analysis) of children with SMA2 and to assess their residual difference from age- and sex-matched controls, after this intervention.

2. Materials and methods

2.1. Subjects

Nine consecutive children with DNA-deletion confirmed SMA2, (four boys, five girls; median age 3.7 years, interquartile range 2.2–4.7), referred to the Respiratory Unit of the Bambino Gesù Research Children's Hospital in Rome, were prospectively enrolled for this study. All children underwent two distinct polysomnographic (PSG) studies. The first PSG study was performed to evaluate the presence and degree of sleep disordered breathing (SDB) and sleep architecture abnormalities, in spontaneous breathing conditions. A subsequent PSG study was performed during LTNPPV. At the time of the subsequent PSG, all children were successfully using LTNPPV from at least four months, with good compliance and their median age was seven years, interquartile range 6.4–8.1.

In addition, 15 age-matched controls (seven boys and eight girls, median age 7.1 years, interquartile range 4.6–8.7) were then recruited from our database of subjects who underwent a polysomnographic study to evaluate sleep disordered breathing but that did not result to be affected by respiratory and/or sleep disturbances.

The local Ethics Committee approved the protocol and the parents of all children gave their written informed consent.

2.2. The long-term non-invasive positive pressure ventilation program

Criteria for LTNPPV were: (a) the presence of recurrent chest infections requiring hospital admission and/or (b) the presence of a large amount of paradoxical breathing or chest wall deformities (as pectus excavatum or bell-shaped chest); (c) presence of significant obstructive sleep apnea (OSA); (d) nocturnal hypoventilation; (f) abnormal deglutition due to dyspnea and/or (g) inability to speak a full sentence without breathlessness [9].

All children were ventilated in a pressure-targeted mode. In details, six children received a pressure support ventilation with a back-up rate (PSV Spontaneous/Timed), and three children received a pressure assist/control ventilation with a back-up rate (APCV). A target volume (8–10 ml/kg) and a back-up respiratory rate were used according to the clinical conditions, weight and age of the children.

All children were treated with nasal vented masks. None of the children included in the study required supplemental oxygen therapy during LTNPPV.

2.3. Study design and procedure

PSG studies were carried out in a quiet room with video monitoring, after one adaptation night that did not include a full PSG set of electrodes, in order to minimize the first-night effect. All recordings started at the patients' usual bedtime and continued until spontaneous awakening.

No hypnotic drugs were allowed for at least two weeks before sleep recording. All patients were accompanied by one of their parents throughout the night.

2.4. Polysomnography and sleep analysis

An overnight PSG assessment was performed using E-series (Compumedics Australia) and PtcCO2 was monitored by SENTEC (SenTec Digital Monitor, SenTec Inc, Therwil, Switzerland).

The EEG recordings and electrode placement were performed according to the 10–20 system and the PSG montage included at least six EEG channels Fp1, Fp2, C3, C4, O1 and O2 (referred to the contralateral mastoid), left and right electrooculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), nasal cannula, thoracic and abdominal respiratory effort (inductance plethysmography), oxygen saturation and transcutaneous partial pressure of carbon dioxide measurements.

The recordings were carried out using a computerized workstation (E-series, Compumedics, Australia) and then scored manually and interpreted according to the current guidelines [10,11].

The PtcCO2-device was calibrated before every measurement and adjusted to the patients PaCO2. No oxygen was supplemented or respiratory stimulants were used.

Sleep was studied into 30-s epochs and sleep stages were scored according to the standard AASM criteria by the American Academy of Sleep Medicine [11]. Awakenings were polygraphically identified by two or more consecutive epochs scored as wakefulness, surrounded by epochs of sleep.

According to Terzano et al. [11], CAP was defined as a periodic EEG activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A), recurring at intervals up to 2 min in duration. The return to background activity identifies the interval that separates the repetitive elements (phase B). In particular, phase-A candidates were scored within a CAP sequence only if they precede and/or are followed by another phase A in the temporal range of 2–60 s. If there were three consecutive A-phases followed by a NCAP (non-CAP) condition, the CAP sequence is stopped at the end of the second B-phase and the third A-phase A is quantified as non-CAP.

We adopted the CAP subtype scoring criteria as follows:

Subtype A1: A phases in which slow EEG synchrony is the predominant activity, mostly comprising high-voltage delta bursts. Phasic activities initiating a phase A must be one-third higher than the background voltage (calculated during the 2 s before the onset and 2 s after the offset of a phase A).

Subtype A2: A phases that contain a mixture of slow and fast EEG activities, including bursts of theta rhythms (associated or not with EMG activation), delta wave bursts followed by theta and other faster rhythms. Moderate increase of muscle tone, cardio-respiratory rate, or both are associated to subtype A2.

Subtype A3: A phases in which the EEG activity is predominantly fast low-voltage rhythms with more than 50% of phase A occupied by fast EEG activities (including EEG arousals), polyphasic bursts and high-voltage delta waves with an amplitude one-third higher or more than the background activity, followed by theta and other faster rhythms.

The following CAP parameters were derived: CAP rate (percentage of total NREM sleep time occupied by CAP sequences), number and duration of CAP cycles, number and duration of CAP sequences, number, duration and percentage of each A phase subtype; A1, A2 and A3 index (number of phases A1, A2 or A3 per hour of NREM sleep), and number and duration of B phases.

2.5. Respiratory events

The apnea/hypopnea events were counted according to the criteria by the American Academy of Sleep Medicine [12]: obstructive apnea (OA) was defined as the absence of nasal airflow with continued chest wall abdominal movements for at least two breaths. Central apnea (CA) was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 s or of shorter duration and associated with an arousal and/or a 3% oxygen desaturation. CA occurring after gross body movements or after sighs were not included in the analysis. Mixed apnea was defined as an apnea that usually begins as central and ends as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in SpO2 of at least 3% and/or an arousal. The apnea-hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of time on bed. For this study, sleep disordered breathing was defined as having an AHI greater than or equal to 1.

All recordings were visually scored by one of the investigators (EV), and the sleep parameters derived were tabulated for statistical analysis.

2.6. Statistical analysis

Because of the relatively low number of patients enrolled and the non-gaussian distribution of data, the nonparametric descriptive statistics were used (median and interquartile range) followed by the Wilcoxon test for paired datasets used for the comparison of the two recording sessions and the Mann–Whitney test for unrelated datasets used for the comparison between sleep architecture and microstructure of SMA2 patients and controls. In order to account for the possible lack of power due to the low number of patients, also the effect size was assessed by means of the Cohen's d (0.2 is indicative of a small effect size, 0.5 of a medium effect size and 0.8 of a large effect size). Differences were considered statistically significant at $p < 0.05$. The commercially available software STATISTICA (data analysis software system), version 6, StatSoft Inc, (2001) was used for all statistical tests.

3. Results

Polysomnography during LTNPPV was performed after a median interval of 2.1 years from the start of the treatment. Table 1 shows age and cardiorespiratory PSG parameters at baseline and after LTNPPV. All cardiorespiratory parameters were found to be improved with AHI significantly reduced, and the minimum SaO_2 significantly increased.

The sleep architecture parameters (Table 2) were only slightly modified on LTNPPV, with an increase in stage N2%, and a decrease in number of awakenings. Table 3 shows that while on LTNPPV, several significant differences persisted between SMA2 patients and controls: decreased sleep period time, total sleep time, number of awakenings, sleep efficiency and percentage of REM sleep, while stage W was increased.

Sleep microstructure, evaluated by means of CAP analysis showed only marginal changes on LTNPPV, reaching statistical significance only for the small shortening of CAP A1 subtype duration and the small increase in CAP subtype A3 index (Table 4). Instead, CAP parameters on LTNPPV in SMA2 patients compared to those of age- and sex-matched controls showed several significant differences: increase in the percentage of A1 and decrease in the percentage of A2 and A3 subtypes, increased duration of A1 and A2 subtypes, decrease A2 and A3 indexes and decreased number of CAP sequences (see Table 5).

4. Discussion

To our knowledge, this is the first study assessing the effects of LTNPPV on sleep architecture and microstructure of children affected by Spinal Muscular Atrophy type 2. In general, data on sleep characteristics of patients treated with long term home mechanical ventilation are incomplete. For the purposes of this study, we considered as long-term non-invasive ventilation a period of at least four months of treatment. Furthermore, we believe that this period is long enough to allow the assessment of the long-term effects on sleep respiratory, architecture and microstructure polysomnographic parameters. However, even if the long time between the basal PSG study and that after LTNPPV allows us to study its long-term effects on sleep respiration and structure, it should also be taken into account that the observed changes might be due, at least in part, to age-dependent physiological maturation [13].

Table 1
Age and cardiorespiratory polysomnographic parameters at baseline and after long term non-invasive positive pressure ventilation.

	Baseline		LTPPV		Wilcoxon	Cohen's d
	median	interquartile range	median	interquartile range	p<	effect size
Age, years	3.4	2.2–4.7	7.0	6.4–8.1	–	–
Mean SaO_2, %	96.0	94.0–98.0	96.0	95.0–97.0	NS	−0.265
Minimum SaO_2, %	87.0	83.0–89.0	91.0	91.0–94.0	0.033	**−1.400**
SaO_2 <90%, %	0.2	0.1–0.3	0.0	0.0–0.0	0.018	0.599
Mean CO_2, mmHg	36.9	35.0–42.0	41.0	37.0–41.0	NS	−0.375
Apnea/hypopnea index, n/hour	3.0	1.2–5.0	0.1	0.0–0.8	0.028	**0.932**
IPAP, cmH_2O			12.0	10.0–14.0	–	–
EPAP, cmH_2O			4.0	4.0–4.0	–	–
Respiratory rate, breaths/min			20.0	18.0–22.0	–	–
LTPPV duration, months			25.0	12.0–38.0	–	–

LTNPPV: long term non-invasive positive pressure ventilation; IPAP: inspiratory airway pressure; EPAP: expiratory airway pressure. Large effect sizes are in bold lettering.

Table 2
Sleep architecture parameters at baseline and after long term non-invasive positive pressure ventilation.

	Baseline		LTPPV		Wilcoxon	Cohen's d
	median	interquartile range	median	interquartile range	p<	effect size
Time in bed, min	524.5	470.0–578.5	510.0	463.5–570.0	NS	0.013
Sleep period time, min	478.0	407.5–497.0	443.5	433.0–465.0	NS	0.365
Total sleep time, min	432.5	345.0–440.5	418.5	371.5–423.5	NS	−0.008
Sleep latency, min	56.5	40.0–61.0	77.5	30.0–103.0	NS	−0.675
Stage R latency, min	83.5	49.0–143.5	142.5	80.0–164.0	NS	−0.320
Awakenings, number/hour	4.0	3.7–5.3	2.8	2.2–3.1	0.03	**1.347**
Sleep efficiency, %	76.9	74.8–79.0	80.0	73.4–83.0	NS	−0.141
Stage W, %	11.4	9.8–14.7	7.0	4.9–16.2	NS	0.641
Stage N1, %	7.1	6.3–11.2	2.4	2.2–5.1	NS	**1.330**
Stage N2, %	36.6	29.0–39.1	46.7	42.6–56.0	0.015	**−1.394**
Stage N3, %	27.5	24.0–34.5	23.4	24.5–25.7	NS	**0.882**
Stage REM, %	12.6	12.1–17.3	16.3	10.8–21.6	NS	−0.205

LTNPPV: long term non-invasive positive pressure ventilation. Large effect sizes are in bold lettering.

Table 3
Sleep architecture parameters after long term non-invasive positive pressure ventilation in SMA2 patients compared to those of age- and sex-matched controls.

	Controls		LTPPV		Mann–Whitney	Cohen's d
	median	interquartile range	median	interquartile range	p<	effect size
Time in bed, min	566.0	540.5–587.5	510.0	463.5–570.0	NS	0.469
Sleep period time, min	540.5	476.0–572.0	443.5	433.0–465.0	0.0016	**1.738**
Total sleep time, min	520.0	476.0–550.0	418.5	371.5–423.5	0.0002	**2.133**
Sleep latency, min	19.5	7.0–41.5	77.5	30.0–103.0	0.005	**−1.182**
Stage R latency, min	118.5	86.0–140.0	142.5	80.0–164.0	NS	−0.188
Awakenings, number/hour	4.8	4.4–6.7	2.8	2.2–3.1	0.00014	**−2.612**
Sleep efficiency, %	93.0	90.2–98.0	80.0	73.4–83.0	0.00054	**2.050**
Stage W, %	0.3	0.0–3.8	7.0	4.9–16.2	0.0007	**−1.675**
Stage N1, %	2.7	1.3–5.3	2.4	2.2–5.1	NS	−0.172
Stage N2, %	49.8	44.4–53.1	46.7	42.6–56.0	NS	0.221
Stage N3, %	23.6	22.1–25.3	23.4	24.5–25.7	NS	0.041
Stage R, %	22.6	18.1–26.0	16.3	10.8–21.6	0.02	**1.085**

LTNPPV: long term non-invasive positive pressure ventilation. Large effect sizes are in bold lettering.

Table 4
Sleep microstructure parameters at baseline and after long term non-invasive positive pressure ventilation.

	Baseline		LTPPV		Wilcoxon	Cohen's d
	median	interquartile range	median	interquartile range	p<	effect size
CAP rate, %	36.4	22.3–46.4	35.5	25.8–39.2	NS	0.287
CAP rate in N1, %	6.1	2.9–10.8	1.1	0.0–14.1	NS	−0.132
CAP rate in N2, %	16.7	12.8–28.7	23.7	13.6–32.0	NS	−0.209
CAP rate in N3, %	65.8	34.7–84.1	57.5	42.8–66.6	NS	0.321
A1 subtype, %	96.9	94.9–97.1	94.2	92.4–95.7	NS	0.131
A2 subtype, %	1.7	0.7–3.1	1.2	1.1–2.0	NS	0.221
A3 subtype, %	2.2	1.9–2.4	4.4	3.1–5.6	NS	−0.477
A1 subtype duration, s	9.0	8.6–10.5	7.9	6.7–8.4	0.02	**1.607**
A2 subtype duration, s	12.8	11.8–13.8	12.7	10.3–13.7	NS	0.272
A3 subtype duration, s	16.9	16.4–18.8	18.1	17.5–18.4	NS	−0.225
A1 index, number/hour	40.5	24.7–58.4	36.7	30.8–52.2	NS	0.165
A2 index, number/hour	0.4	0.3–1.5	0.4	0.2–0.7	NS	0.040
A3 index, number/hour	0.5	0.2–1.4	0.9	0.7–1.2	0.02	−0.557
B phase duration, s	24.1	23.2–26.4	24.3	23.7–28.6	NS	−0.120
CAP cycle duration, s	34.0	32.6–35.5	32.9	31.2–35.8	NS	0.373
CAP sequence duration, s	338.6	214.8–359.8	278.8	191.3–345.0	NS	0.236
Number of CAP sequences	24.0	23.0–29.0	23.0	23.0–28.0	NS	0.366

LTNPPV: long term non-invasive positive pressure ventilation. Large effect sizes are in bold lettering.

Our study shows that the number of awakenings decreases, and stage N2 increases significantly in SMA2 patients during LTNPPV and this is in agreement with a previous report that non-invasive ventilation in SMA patients leads to an improvement in sleep architecture in terms of reduced light sleep and increased deep sleep [14]. Furthermore, we observed also a positive effect of LTNPPV on the maintenance of respiratory functions with an improvement in AHI and in minimum SaO_2, similarly to other reports in the literature [14]. However, the LTNPPV long-term effects on respiratory and sleep parameters that have been already reported were obtained from a miscellaneous of neuromuscular disorder patients [14] and not from a homogeneous group with the same disease, as in our study.

Other than the above general considerations, the novelty of the present study is the analysis of sleep microstructure that shows the occurrence of only minimal differences in CAP parameters between

Table 5
Sleep microstructure parameters after long term non-invasive positive pressure ventilation in SMA2 patients compared to those of age- and sex-matched controls.

	Controls		LTPPV		Mann–Whitney	Cohen's d
	median	interquartile range	median	interquartile range	p<	effect size
CAP rate, %	29.6	22–39.7	35.5	25.8–39.2	NS	−0.282
CAP rate in N1, %	15.7	5.0–27.7	1.1	0.0–14.1	NS	0.378
CAP rate in N2, %	20.5	15.9–33.8	23.7	13.6–32.0	NS	0.047
CAP rate in N3, %	43.9	31.9–52.6	57.5	42.8–66.6	NS	−0.596
A1 subtype, %	81.1	58.6–86.8	94.2	92.4–95.7	0.0004	**−1.645**
A2 subtype, %	8.1	6.3–21.7	1.2	1.1–2.0	0.00085	**1.621**
A3 subtype, %	9.6	6.0–15.6	4.4	3.1–5.6	0.0042	**1.390**
A1 subtype duration, s	5.4	4.8–6.5	7.9	6.7–8.4	0.0029	**−1.582**
A2 subtype duration, s	9.0	8.2–10.7	12.7	10.3–13.7	0.0026	**−1.642**
A3 subtype duration, s	16.4	14.6–21.2	18.1	17.5–18.4	NS	−0.092
A1 index, number/hour	36.8	18.0–44.4	36.7	30.8–52.2	NS	−0.298
A2 index, number/hour	3.6	2.3–6.5	0.4	0.2–0.7	0.00075	**1.640**
A3 index, number/hour	2.2	1.5–4.0	0.9	0.7–1.2	0.016	**1.042**
B phase duration, s	24.5	22.0–25.4	24.3	23.7–28.6	NS	−0.420
CAP cycle duration, s	30.4	29.6–33.5	32.9	31.2–35.8	NS	−0.595
CAP sequence duration, s	206.6	140.7–229.8	278.8	191.3–345.0	NS	−0.594
Number of CAP sequences	39.0	25.0–43.0	23.0	23.0–28.0	0.037	**1.254**

LTNPPV: long term non-invasive positive pressure ventilation. Large effect sizes are in bold lettering.

the basal and LTNPPV recordings. This might indicate that the sleep microstructure abnormalities found in our SMA2 patients are not dependent (at least to a large extent) on the sleep disordered breathing but indicate an intrinsic sleep mechanism dysfunction. However, the small changes observed deserve attention and interpretation.

In our previous reports, we already studied the sleep characteristics of SMA1 and SMA2 patients in spontaneous breathing, and we showed a significant disruption of sleep architecture and of CAP microstructure parameters [4,15]; in detail, we found a reduction in the percentage of A3 phases, comparable to a decrease of EEG arousals. We interpreted these findings as a central nervous system involvement in SMA2 patients causing a partial failure to arouse.

In this study, the LTNPPV intervention determined a shortening of CAP A1 subtype duration and an increase in CAP A3 index. The slight increase of A3 index probably reflects the fact that LTNPPV is able to increase the arousability of SMA2 patients approaching the level of arousability of normal controls even if it still remains lower. This finding reinforces the hypothesis that, in these patients, hypoarousability is linked to the SMA condition and is therefore disease-dependent, and only partially linked to the respiratory pattern.

The sleep and arousability abnormalities in patients with SMA, also observed in this study, might be mediated by changes in the central nervous system. In human SMA, low levels of the ubiquitously expressed SMN protein result in the degeneration of lower motor neurons, but it remains unclear whether other regions of the nervous system are affected [16,17]. It has been hypothesized that reduced levels of SMN expression may have effects on non-motor regions of the nervous system. Data derived from animal studies show that high levels of SMN protein are required for a normal brain development in vivo. As a result, a reduced expression of the SMN protein - down to levels sufficient to cause a severe form of SMA in mice - cause abnormal brain development, particularly affecting regions like the hippocampus [18]. Further studies are needed to clarify this issue.

Only few studies have evaluated the effects of non-invasive ventilation on CAP variables. A study on continuous positive air pressure (CPAP) titration in adult patients with obstructive apnea reported that, in order to correct all respiratory flow limitations and to reach an optimal pressure adjustment, it is important to take into account the modification of CAP parameters, especially in NREM CAP periods (and REM sleep) because during non-CAP periods a false titration success might be obtained [19]. Another study evaluated the immediate (first night) and long-term (after 30 days) recovery process of sleep in patients with sleep apnea after CPAP treatment; which demonstrated that the application of CPAP immediately induced a reduction of light sleep, an enhancement of deep sleep and a reduction of CAP rate [20]. However, the amount of CAP cycle and A1 subtypes remained below control values even after one month of sustained treatment [20]. This last finding is in agreement with our data reporting relatively small (but important) changes in CAP parameters that can allow us to better understand the pathophysiology of the specific disease.

Our study has several limitations, sleep microstructure parameters were not used as an integrative outcome to set and adjust the non-invasive ventilation setting; the non-invasive ventilation were set in order to normalize nocturnal breathing patterns, preventing desaturation and improving gas exchange during sleep. Another limitation regards the small number of patients, although this factor is closely related to the fact that SMA is a rare disease. There is a need for polycentric studies in order to collect larger groups of SMA patients and better define their specific sleep patterns in basal conditions and during LTNPPV.

5. Conclusions

This seems to be the first study in children affected by SMA2 reporting data on sleep microstructure (CAP) and their changes after long-term non-invasive ventilation. We found small but important changes in sleep microstructure during LTNPPV in these children, probably suggesting that this treatment partially improves their arousability. Further studies are needed to understand if this is due to the natural course of the underlying disease and if sleep architecture and CAP modifications might be considered as a disease marker useful to evaluate the clinical evolution and to control the adequate setting of ventilators.

Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.005.

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