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Original Article

Sleep architecture in children with spinal muscular atrophy type 2

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ABSTRACT

Objective: There have been few published reports on the sleep patterns of patients with spinal muscular atrophy (SMA) type 2, and none on sleep microstructure. The aim of this study was to analyze sleep architecture and microstructure in a group of children with SMA type 2, compared with age-matched and sex-matched controls.
Methods: Seventeen SMA type 2 children (seven males, mean age 4.2 years) and 12 controls (five males, mean age 5.0 years) underwent full polysomnography to evaluate sleep architecture and microstructure by means of the Cyclic Alternating Pattern (CAP).
Results: Compared with the control children, the SMA type 2 patients showed a mild increase in the apnea/hypopnea index. Sleep was characterized by a decrease in the number of sleep stage shifts per hour, of percentage of stage N3, of stage R, and of sleep efficiency. On the contrary, significant increases of awakenings per hour, wake after sleep onset, and percentage of stage N1 were found. The CAP analysis revealed a significant increase in the percentage of A1 CAP subtypes, a reduction of that of A3 subtypes, and of A2 and A3 indexes.
Conclusions: The results indicated an abnormality of sleep macrostructure and microstructure in SMA type 2 patients, which was characterized by a reduction of A2 and A3 subtypes (low and high power arousals), supporting the concept of a decreased arousability in SMA type 2 patients. Similar to a previous report on SMA type 1, the findings might be additional proof of central nervous system involvement, although these alterations are less severe than those observed in infants with SMA type 1.

1. Introduction

For people with neuromuscular diseases, sleep changes are important not only because of the cardiorespiratory aspects but also for the modifications of sleep stage architecture. 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 gene responsible for SMA has been located within the complex genomic region at chromosome 5q11.2–q13.3, which contains a 500-Kb inverted duplication [4,5].

The phenotype expression of the disease is inversely proportional to the amount of complete survival motor neuron 1 (SMN1) protein, and ranges from severe generalized paralysis and need for ventilator support from birth to relatively mild conditions presenting in young adults. In children that present with significantly more sleep apnea and thoraco-abdominal asynchrony during the inspiratory and expiratory phases in both quiet and active sleep, sleep breathing disorders are an additional cause of morbidity and impaired quality of life [6].

There are very few studies on sleep patterns in patients with SMA [7]. In a polysomnographic study of 32 neuromuscular patients, four of which had a form of SMA, sleep architecture revealed an increase of stage 1 sleep, coupled with a decrease or absence of REM sleep [8].

Another study on seven children with SMA (six with SMA type 1.5–1.8, one with SMA type 2) showed impaired sleep architecture, but compensated nocturnal and diurnal gas exchange. In these cases, nocturnal non-invasive ventilation (NIV) resulted in a significant improvement in sleep architecture with higher sleep efficiency, decreased light sleep counterbalanced by increased deep sleep, longer rapid eye movement (REM) sleep, and significantly less electroencephalogram (EEG) arousals [9]. In a recent study on SMA type 1, abnormal sleep microstructure was reported, postulating that SMA type 1 patients have reduced arousability during non-rapid eye movement (NREM) sleep [10].

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Since no specific research on sleep structure is available for SMA type 2 children, the aim of the present study was to evaluate sleep architecture in a group of children with SMA type 2, together with an analysis of sleep microstructure by means of Cyclic Alternating Pattern (CAP), compared with an age-matched and sex-matched control group.

2. Methods

2.1. Subjects

The present study included 17 children with DNA-deletion confirmed SMA type 2 referred to the Respiratory Unit of the Bambino Gesù Research Children's Hospital in Rome (seven males; mean age 4.2 years; 2.39 SD years) and 12 age-matched controls (five males; mean age 5.0 years; 1.18 SD years). Controls were recruited from a database of subjects who underwent a polysomnographic study to evaluate sleep disordered breathing, but that did not result in being affected by respiratory and/or sleep disturbances.

Exclusion criteria for controls were: (1) a neurological or genetic disorder or craniofacial anomaly; (2) abnormal growth or development; (3) history of seizures; (4) pre-existing lung disease; and (5) any sign of respiratory tract infection within the last two weeks.

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

2.2. Polysomnography

Polysomnographic studies were carried out for both groups (patients and controls) in a quiet room with video monitoring. They were carried out after one adaptation night that did not include a full polysomnography set of electrodes, in order to minimize the first-night effect. All recordings started at the patients' usual bedtimes and continued until spontaneous awakening. No hypnotic drugs were allowed for at least two weeks before sleep recording. All children were accompanied by one of their parents throughout the night.

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); electromyogram of left and right tibialis anterior muscles; nasal cannula; thoracic and abdominal respiratory effort (inductance plethysmography); oxygen saturation; and transcutaneous partial pressure of carbon dioxide (TCM 4, Radiometer, Copenhagen, Denmark) 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 [11,12]. The PtcCO2 device was calibrated before every measurement and adjusted to the patients PaCO2. No oxygen was supplemented, nor were any respiratory stimulants used.

Sleep was subdivided into 30-second epochs, and sleep stages were scored according to the standard criteria of the American Academy of Sleep Medicine (AASM) [12]. Awakenings were polygraphically identified by two or more consecutive epochs scored as wakefulness, and surrounded by epochs of sleep.

According to Terzano et al. [13], the 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 minutes in duration. The return to background activity identified the interval that separated the repetitive elements (phase B). In particular, phase-A candidates were scored within a CAP sequence only if they preceded and/or were followed by another phase A in the temporal range of 2–60 seconds. If there were three consecutive A phases followed by a NCAP condition, the CAP sequence was stopped at the end of the second B phase, and the third A-phase A was quantified as non-CAP.

In the present study, the following CAP subtype scoring criteria for infants was adopted:

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

The apnea/hypopnea events were counted according to the criteria established by the American Academy of Sleep Medicine manual (AASM 2007) [12] and the American Thoracic Society [11]: an obstructive apnea was defined as the absence of airflow, with continued chest wall and abdominal movement, for a duration of at least two breaths; a mixed apnea was defined as an apnea that usually begins as central and ends in obstruction, according to changes in the chest, abdominal, and flow traces; hypopnea was defined as a decrease in nasal flow of at least 50% and associated with a decrease in SaO2 of at least 3%, awakening or arousal; the apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST). For the present study, sleep disordered breathing was defined as having an AHI ≥1.

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

2.3. Spirometry

According to the current published guidelines [14], spirometry was obtained in patients >6 years of age due to the lack of cooperation of younger children in performing the test.

2.4. Statistical analysis

The age and respiratory parameters of the subjects of the two groups were compared by means of the Student's *t*-test, while sleep stage architecture and CAP parameters were compared by means of the Analysis of Covariance (ANCOVA) using age as a covariate. 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

No differences were found in patient group composition with respect to gender: in SMA type 2 there were seven males (41.1%),