Original Article

Isolated rapid eye movement sleep without atonia in amyotrophic lateral sclerosis

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ABSTRACT

Objective: The aim of this study was to quantitatively analyze, with the most recent and advanced tools, the presence of periodic leg movements during sleep (PLMS) and/or rapid eye movement (REM) sleep without atonia (RSWA), in a group of patients with amyotrophic lateral sclerosis (ALS), and to assess their eventual correlation with the clinical severity of the disease.
Methods: Twenty-nine ALS patients were enrolled (mean age 63.6 years) along with 28 age-matched "normal" controls (mean age 63.8 years). Functional impairment due to ALS was evaluated using the ALS-Functional Rating Scale-Revised (ALS-FRS) and the ALS severity scale (ALSSS). Full video polysomnographic night recordings were obtained, and PLMS were analyzed by considering their number/hour of sleep and periodicity index, the distribution of intermovement intervals, and the distribution during the night. The characteristics of the chin electromyogram (EMG) amplitude during REM sleep were analyzed by means of the automatic atonia index and the number of chin EMG activations (movements).
Results: The ALS patients showed longer sleep latency than the controls, together with an increase in number of stage shifts, increased sleep stage 1, and decreased sleep stage 2. None of the leg PLMS parameters were different between the ALS patients and controls. The REM atonia index was significantly decreased in the ALS patients, and the number of chin movements/hour tended to increase. Both REM atonia index and number of chin movements/hour correlated significantly with the ALS-FRS; REM atonia was higher and chin movements were less in ALS patients with more preserved function (higher scores on the ALS-FRS).
Conclusion: Abnormal REM sleep atonia seemed to be a genuine effect of ALS pathology per se and correlated with the clinical severity of the disease. It is unclear if this might constitute the basis of a possible risk for the development of REM sleep behavior disorder or represent a form of isolated RSWA in ALS.
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1. Introduction

Amyotrophic lateral sclerosis (ALS), or Charcot or Lou Gehrig's disease, is an adult-onset progressive and fatal neurodegenerative disease. It is characterized by rapid and progressive loss of cortical, spinal, and bulbar motor neurons, with consequent paralysis of striatal skeletal and bulbar muscle, dysphagia, dysarthria, and respiratory impairment resulting in terminal respiratory failure, which is the most common cause of death [1,2] and usually occurs within one to five years from onset.

Patients with ALS often report disturbed sleep and, in the past, particular attention has been paid to the chronic nocturnal respiratory insufficiency and hypoventilation that inevitably occur during the clinical course of this disease, and that anticipate the onset of respiratory failure [3–5]. The majority of cases of ALS are sporadic, but about 5–10% are familial, with an autosomal dominant inheritance pattern due to mutations in specific genetic loci [6,7].

Sleep in patients affected by ALS may be disturbed by several factors, namely sleep disordered breathing, nocturia, sleep fragmentation, nocturnal cramp, pains, depression, poor mobility, difficulty changing position, increased salivation, and problems with swallowing [5,8–14].

Few complete overnight polysomnographic sleep studies have been performed, and have usually only been in small patient series. The features that have been more often reported are: difficulties in initiating and maintaining sleep, long sleep latency, reduced sleep

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efficiency, increased sleep stage 1, and shorter rapid eye movement (REM) sleep [5,15–17]. However, it is unclear if the sleep architecture changes that have been found correlate with the clinical severity of ALS.

In particular, the motor activity during sleep has not often been assessed and reported in ALS patients; periodic leg movements during sleep (PLMS) have sometimes been grossly analyzed [18–20] and the possible presence of REM sleep behavior disorder (RBD) has been suspected in only a few single case reports [17,21,22], but REM sleep without atonia (RSWA) has not been quantitatively assessed.

The aim of the present study was to quantitatively analyze, with the most recent and advanced tools, the presence of PLMS and/or RSWA in a group of patients with ALS without restless legs syndrome (RLS) or RBD, and to assess their eventual correlation with the clinical severity of the disease.

2. Subjects and methods

2.1. Subjects

Twenty-nine consecutive ALS patients were enrolled in the study (10 women and 19 men, mean age 63.6 years, 11.61 SD) at the Sleep Center, Neurophysiology Unit of the University of Cagliari. Exclusion criteria were: being aged <18 years, patients that denied consent, and patients with severe clinical conditions that did not allow one night in the sleep lab. However, none of the patients who were considered fell into these exclusion categories during the study. Detailed clinical data of the patients were collected, which allowed their diagnosis as definite or probable ALS, according to the El Escorial World Federation of Neurology revised criteria [23]. Functional impairment due to ALS was evaluated using the ALS-Functional Rating Scale-Revised (ALS-FRS) and the ALS severity scale (ALSSS) [24].

In order to exclude dementia and fronto-temporal dementia, in particular, the cognitive status of the patients was carefully assessed by means of a neuropsychological test battery, including: Minimental state examination [25], Frontal assessment battery [26], Neuropsychiatric Inventory [27], Rey auditory verbal learning [28], Rey complex figure [29], Corsi forward and backward block-tapping [30], Semantic and Phonemic Category fluency [31], Benton judgment of lines orientation [32], BADA battery test for the evaluation of aphasia deficit [33], and the Hamilton rating scale for depression [34].

Finally, the presence of the Cu/Zn superoxide dismutase 1 (SOD1), transactive response DNA-binding protein of 43 kD (TARDBP), fused in sarcoma (FUS), and c9ORF72 gene mutations were tested in these patients, following standard procedures [35].

The control group was formed by 28 drug-free, age-matched "normal" controls (12 women and 16 men, mean age 63.8 years, 12.19 SD), without clinical evidence of sleep or other major neurological/psychiatric disturbances.

In order to formally detect and exclude the eventual presence of specific sleep disorders, such as RLS [36] or RBD [37], all patients and controls were carefully assessed by a certified expert in sleep disorders.

This study was approved by the local ethics committee (approval no. 2013/3205). Before entering the study, all subjects provided informed consent according to the Declaration of Helsinki.

2.2. Polygraphic sleep recordings

Each patient underwent a full video polysomnographic night recording, after an adaptation night, carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory. The controls did not have video recordings during polysomnography. Subjects were not allowed to have beverages containing caffeine during the afternoon preceding the recording, and were allowed to sleep until their spontaneous awakening in the morning.

The following parameters were included in the polysomnographic study: electroencephalogram (EEG) (at least three channels, one frontal, one central, and one occipital, referred to the contralateral earlobe), electrooculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1), electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg), and electrocardiogram (ECG) (one derivation). The sleep respiratory pattern of each patient was assessed by means of oral and nasal airflow (thermistor and/or nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge), and oxygen saturation (pulse-oxymetry) in a previous recording (within one week) or during the study night. Sleep signals were stored on hard disk in European data format for further analysis.

2.3. Sleep scoring, analysis of leg movements, and assessment of the chin EMG amplitude during REM sleep

Sleep stages were scored following standard criteria [38] on 30-second epochs by means of the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). Leg movements (LMs) during sleep were first detected by the same software. With this software, the detection is performed by means of a human-supervised automatic approach that is controlled by the scorer. The performances of this system have been evaluated and validated [39]. For the present study, one scorer (RF) visually edited the detections proposed by the automatic analysis, before the computation of the LM parameters, which were automatically generated by the same software, adopting the criteria set by the International RLS Study Group and endorsed by the World Association of Sleep Medicine [40].

The standard PLMS (sPLMS) index was calculated, following the above criteria, as the number of LMs included in a series of four or more, separated by >5 and >90 s/hour of sleep. Additionally, the number of intermovement intervals that were 10–90 s long, and all in sequences of at least three, was divided by the total number of intervals to yield the Periodicity index; this index can vary between 0 (absence of periodicity, with none of the intervals having a length between 10 and 90 s) and 1 (complete periodicity, with all intervals having a length between 10 and 90 s) [41,42]. The Periodicity index was independent on the absolute number of LMs recorded and was calculated for all nights included in this study. Additionally, a recently introduced, alternative PLMS index that more closely reflects the "genuine" periodic portion of LMs was also calculated [43]. The alternative PLMS (aPLMS) index adopts the same criteria as the sPLMS index, but considers only LMs separated by ≥10 s and ≤90 s and, differently from the standard rules [40,44], interrupts a possible PLMS series if the interval between two consecutive LMs is <10 s [43].

The characteristics of the chin EMG amplitude during REM sleep were analyzed by means of an automatic quantitative approach (atonia index) [45,46]; mathematically, this index can vary from 0 (ie, complete absence of EMG atonia) to 1 or stable EMG atonia. Also, the number of chin EMG activations (movements) was counted in REM sleep. In order to avoid the inclusion of respiratory-associated activities in REM sleep into the atonia index calculation, a blinded sleep expert neurophysiologist (PC) visually checked the muscle tone and eliminated respiratory arousal-related muscle tone increases. Furthermore, the reliability of the atonia index calculation has also previously been validated in OSA patients [46,47].

2.4. Statistical analysis

For the statistical analysis, all comparisons between patients and controls were performed by means of the Student's t-test, followed by the Bonferroni correction for multiple comparisons.