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TITOLO TESI

ASSESSMENT OF CARDIAC AUTONOMIC NERVOUS SYSTEM DURING SLEEP AND SLEEP STABILITY IN PATIENTS AFFECTED BY AMYOTROFIC LATERAL SCLEROSIS

Settore/i scientifico disciplinari di afferenza

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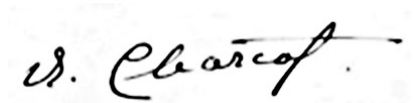Coordinatore Dottorato: Prof. Francesco Marrosu

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"Disease is very old, and nothing about it has changed. It is we who change, as we learn to recognize what was formerly imperceptible'"

J.M. Charcot

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ABSTRACT

Objective: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease, associated with an almost exclusive involvement of upper and lower motor neurons, although autonomic impairment has also been described. Often patients affected by ALS complain of disturbed sleep and sudden death during sleep has been reported. To date, few overnight polysomnographic studies have been performed and a complete evaluation of autonomic nervous system (ANS) during sleep has never been performed before in ALS subjects. The aim of our study was to assess macro- and microstructure of sleep, detect any sleep disorders and evaluate cardiac ANS in a cohort of ALS patients, in order to better characterize the disease and identify novel strategies to improve quality of life and possibly prolong life expectancy.

Methods: 23 patients affected by ALS (16M/7 F, age 26-79, mean 61) were compared to 15 healthy controls matched for age and sex. Each subject underwent a full-night video-polysomnography. Sleep staging was performed according to AASM criteria, assessment of sleep stability was made by means of both CAP detection and CPC (cardiopulmonary coupling), evaluation of ANS was made with assessment of HRV.

Results: Compared to controls, ALS patients showed a significant reduction of sleep efficiency and of total sleep time, longer sleep latency than controls, together with an increased number of WASO, increased N1 sleep and decreased N2, N3 and REM sleep. Moreover patients showed a significant reduction of CAP rate mainly due to a significant reduction in phase A1 and A2. Compared to controls, patients showed significant reductions in: total HRV power during non-

REM (p=0.005), LF in non-REM (p=0.01) and REM (p=0.003) sleep, and wake after sleep onset (WASO) (p=0.06) and also in HF during non-REM (p=0.04) and REM (p=0.05) sleep and WASO (p=0.03). CPC analysis showed the patients with the most advanced pathology, i.e. those with ALS-FRS<30, had the most unstable sleep patterns, with high percentage of LFC and low percentage of HFC (<4%).

Interpretation: Our results confirm that sleep structure and stability of ALS patients is altered, and that there is a subclinical alteration of cardiac autonomic control in both sleep and wakefulness, with an impairment of both vagal and sympathetic systems. Moreover reduction of CAP rate, analogously to the reduction of HRV, may reflect an alteration of cortical circuits wich underlie to the organization of sleep and autonomic functions, which are strongly interconnected, that in these patients seem to be characterized by a marked rigidity, with poor reactivity and reduced adaptability to external or internal stimuli. These findings suggest the potential importance of assessment of autonomic nervous system and sleep in ALS, in conjunction with standard motor system evaluations.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou gehrig disease o Charcot's disease, is a inexorably progressive, devastating and fatal neurodegenerative disease, characterized by progressive degeneration of spinal, bulbar and cortical motor neurons and consequent painless paralysis of striatal skeletal and bulbar muscle with dysphagia, dysarthria and respiratory impairment. So far there are not effective therapies and the death occurs usually within 2-3 years after disease onset, typically for respiratory failure[1,2].

Classically ALS is considered a pure motor neuron disease, and concomitant presence of symptoms and signs involving cognitive domain, sensory, cerebellar and autonomic systems suggests alternative diagnoses[3,4]. Today the evidence of concomitant involvement of other systems, including autonomic nervous system, is documented in ALS[5].

Sleep fragmentation and sleep disorders may be an early manifestation of ALS, although underdiagnosed. Several factors may disturb sleep in ALS patients, namely sleep disordered breathing, nocturia, sleep fragmentation, restless legs syndrome, nocturnal cramps, pain, depression, poor mobility, difficult in changing position, increased salivation and problems in swallowing and difficult cough[6–8]. Particular attention has been paid to the chronic nocturnal respiratory insufficiency and hypoventilation[9] that commonly anticipate the onset of awake respiratory failure due to the physiologic vulnerability of respiration during sleep and it is well-known that non invasive ventilation (NIV) increase survival in patients affected by ALS[6,9].

There are many well-documented cases of patients diagnosed with ALS who presented extramotor symptoms[5,10], including autonomic dysfunction[11], namely cardiovascular manifestations[11], altered sweat[12–15], impaired salivary[16,17] and lacrimary secretions[18], alteration of urinary[19] and gastrointestinal function[20–22]. Cardiovascular disfunction in ALS has been reported[23–28], especially in advanced stages of the disease and during sleep; moreover altered cardiac autonomic control with predominance of sympathetic system and depresses parasympathetic function have been documented[11,28], and sudden death and cardiovascular dysfunction due to dysautonomia are probably more frequent during sleep in these patients[11]. Alterations of ANS as reduced heart rate variability (HRV) and increased sympathetic tone have been identified as mortality risk factors in patients with cardiac diseases[11,29].

To date few overnight polysomnographic studies have been performed in patients affected by ALS[8,30], and a complete evaluation of autonomic nervous system (ANS) during sleep, with regard to each sleep stage (NREM-N1-N2-N3 and REM) and wakefulness, has never been performed before in these subjects.

The aim of our study was to evaluate nocturnal sleep of patients affected by ALS, in order to assess sleep quality, sleep stability, sleep respiratory function and autonomic function during both sleep and wakefulness. In particular we assessed ANS in wakefulness, NREM (light and deep) sleep and REM sleep, through HRV evaluation by means of a single-lead ECG, recorded during Polysomnography (PSG). Moreover we evaluated sleep stability, with CAP detection[31], and also with Cardiopulmonary Coupling (CPC)[32,33].

Autonomic Nervous System assessment

Heartbeat is a vital function; the number of beats per minute (BPM) is defined heart rate (HR). HR is not constant, but subject to a range oh physiological fluctuations, and the inter-beat difference, or R-R interval, is employed to quantify the Heart rate variability (HRV). The most important regulator of cardiac electrical activity is ANS, with opposite reaction by sympathetic and parasympathetic (vagal) system, the first increasing HR, the second decreasing it, up to well-regulate cardiac activity, in relation to internal and external stimuli[34,35]. Factors that may modify HR are: respiration, blood oxygen, physical activity, mood, thinking, mental stress, drugs and substances, sleep. In a healthy person heart rate presents a physiological variability, that reflects a good adaptability of cardiovascular system to continuous external and internal changes[36,37].

HRV assessment permits to get information about sympatho-vagal balance, that reflects the adaptability of ANS. Higher HRV is typically a sign of good adaptation and is typical of a healthy person, while lower HRV is an indicator of reduced adaptability and reflects an alteration in autonomic responses[38].

HRV analysis is used as a simple and non-invasive diagnostic tool to study ANS through measure of vagal and sympathetic oscillations both in physiological and pathological conditions. Decreased HRV has been found in several pathological conditions, not only of cardiovascular system, namely coronary artery disease, cardiomyopathy, arterial hypertension, myocardial infarction, heart failure, smoking, obesity, chronic obstructive pulmonary disease, renal failure, diabetes, stroke, Alzheimer's disease, leukemia, obstructive sleep apnea, epilepsy,

headache, among other[38]; and it has been described that decreased HRV is a predictor of mortality, even in ALS patients[11].

HRV evaluation is based on the assessment of rhythmical oscillations of heartbeats, which represent the sympathetic and vagal modulations of cardiovascular function.

For HRV analysis linear and non-linear methods may be used; linear methods including time-domain and frequency-domain parameters[39].

The main parameters obtained by time-domain analysis of HRV are statistical and geometrical (see table 1 and table 2 for details)[36].

Statistical measures are: averageNN, SDNN, SDANN, RMSSD, SDNN index, NN50 and pNN50.

Geometrical measures are: HRV triangular index and TINN.

The main parameters obtained by frequency-domain analysis of HRV are: total power spectrum, ULF, VLF, LF, HF, LFnu, HFnu, LF/HF[36].

The VLF component is considered to be a marker of humoral and hormonal fluctuations; the HF component is considered a marker of vagal modulation, while it is still debated whwther the LF component represents a marker of both sympathetic and vagal modulation or if it is a marker of sympathetic activation[39,40].

In addition nonlinear/entropy/complexity measures are valuable, typically employed on longer time scales to help define multiscale features of time series, and the amount of informatio needed to describe them[41,42].

Autonomic function during sleep

Autonomic Nervous System activity is influenced by sleep and it changes continuously during sleep in relation to different sleep stages. Moreover neuronal populations involved in sleep-wake control are localized near the areas involved in cardiovascular control, and they are reciprocally interconnected and integrated also with central autonomic influences and cardiovascular reflexes. These connection and integrations cause sleep-related changes in cardiovascular function[34,35]. In particular sympathetic activity progressively decreases from wakefulness to deep sleep, and parasympathetic tone is predominant during the whole sleep. For these reasons heart rate (HR) and blood pressure (BP) tend to decrease during physiological NREM sleep, with the minimum levels in N3; baroreflex (BR) is maximally reduced and HR is maintained slow despite reduced BP. Moreover in NREM, every 20-30 seconds, we can observe increases of HR and BP, associated to changes in EEG activity (alpha rhythm, K-complexes, Slow Waves), or suddenly as a response to an arousing stimuli. In REM sleep there is a predominance of sympathetic activity, with HR and BP values analogous to those in wakefulness. In REM sleep BR presents a not-uniform behavior, with different responses to hypertensive and hypotensive stimuli. Moreover during REM sleep we can observe transient HR and BP increases in association with bursts of REMs and muscle twitches[34].

The microstructure of sleep- The Cyclic Alternating Pattern (CAP)

EEG activity during NREM sleep presents physiologically continuous fluctuations, which are known as Cyclic Alternating Pattern (CAP), consist of

arousal-related phasic events, and sets up the microstructural organization of sleep, reflecting the continous oscillations of arousal levels. CAP is organized in sequences, and each CAP sequence is made of cycles, and each single CAP cycle consists of one A phase, characterized by bursts of sleep phasic events (e.g. Delta bursts, Vertex sharp transient, K-complex, intermittent alpha…), followed by a B phase, which represents the return to EEG background. In relation to the EEG feature of phase A, we can distinguish three different types of phase A (A1, A2, and A3). All CAP seqeunces begin with a phase A and end with a phase B. Both A and B phases are 2-60 seconds in duration. The absence of CAP for more than 60 seconds is named NCAP (non-CAP). At least two consecutive CAP cycles are needed to define a CAP sequence. A CAP sequence is not interrupted by a stage shift within NREM sleep, so a CAP sequence may contain different sleep NREM stages. The ammount of CAP sequencies tipically increases immediately before the transition from NREM to REM sleep, and end just before REM begins. Infact, CAP is characterized by global involvement of cortex and thus EEG synchronization is a typical feature; in contrast REM sleep in characterized by asynchronous EEG, thus phase A are observed in REM sleep only in pathological conditions (e.g. concurrently with phasic respiratory events), and consist of desynchronized patterns. The number of CAP sequences per hour of NREM sleep is named CAP rate[31]. CAP is normally present in all subjects and presents modifications in relations to age, and it may be elicited by external factors (e.g. sounds, tactile stimulation) and sleep disorders, namely OSA (obstructive sleep apnea) and PLMs (periodic limb disorders). It plays a fundamental role in the structural organization of sleep, and it involves not only cerebral activities, but it

present a reciprocal influence with ANS and motor functions, with activation of these systems during phase A and deactivation during phase B. CAP is an EEG marker of sleep stability, and it also reflects the capacity of brain to respond to internal and external stimuli also during sleep[43–45]. High CAP rate is an indicator of altered or disturbed sleep, and for this reason it is used in clinical practice in addition to standard sleep scoring.

Electrocardiogram-based Cardiopulmonary Coupling (CPC)

Electrocardiogram (ECG)-based cardiopulmonary coupling (CPC) provides a graphical and computational method to represent the behavior of dynamical interactions between the cardio-autonomics and respiration during sleep. Introduced by Thomas, Goldberger and Colleagues[32,33]. CPC combines spectral information derived from inter-beat interval (R-R) time series and an ECG-derived respiratory signal. The method reveals two distinct modes of cardiopulmonary interaction during non-REM sleep: one in the low frequency band (0.01-0.1 Hz) and the other in the high frequency band (0.1-0.4 Hz). These modes are termed Low Frequency Coupling (LFC) ad High Frequency Coupling (HFC). During REM sleep or wakefulness, the coupling mode is in the very low frequency band (0-0.01 Hz), and is termed Very Low Frequency Coupling (VLFC). LFC reflects unstable (with more arousals) sleep, while HFC reflect stable (deeper) sleep[32,33,46]. The LFC/HFC classification has been found to correlate with the CAP/NCAP classification, while showing low agreement with standard sleep staging[32]. Sleep is considered an ideal condition for probing HRV,

because autonomic function is less influenced by confounding factors, such as movement and activity, and recording is less prone to movement artifacts.

METHODS

1. **Subjects:** Inclusion criteria for the whole study were: age > 18 years, diagnosis of ALS and informed consent. Exclusion criteria for the whole study were: pregnancy, age < 18 years, and failure to sign an informed consent. Exclusion criteria for HRV-CPC assessment were: alterations of heart rhythm, coronary artery disease, heart failure, diabetes, major depressive disorder, serious diseases kidney or liver disease, cancer, cardioactive drugs (e.g. beta-blockers, beta-agonists calcium-channels-blockers, antiarrhythmic drugs, SSRI and atypical antidepressants, atypical antipsychotics, AchE inhibitors, alpha receptors agonists and antagonists).

   The study has been approved by local ethical committee.

   Patients: 24 patients (17 M, 7 F) affected by Amyotrophic Lateral Sclerosis referred to outpatients ALS service – University of Cagliari were consecutively enrolled. One initially enrolled subject did not enter the study for dead. Three patients were excluded from analysis for total sleep time (TST) < 4 hours. The remaining 20 patients were evaluated for HRV assessment, and among these, 13 (8 M, 5 F) were selected for the study and 7 were excluded: 2 because of severe OSAS and 5 for artifacts in the ECG, that interfered with a correct evaluation of HR.

   Controls: 15 volunteer healthy control subjects age and sex matched with patients were enrolled.

2. **Clinical evaluation:** All subjects underwent a thorough history, both about general conditions and sleep, neurological examination and questionnaires specific for sleep and its disorders, namely Epworth sleepiness scale (ESS),

Pittsburgh Sleep Questionnaire Index (PSQI), Berlin Questionnaire Index (BQI), Restless Legs Syndrome Severity Scale (RLSSS), Rem Behavior Disorder Index (RBDI) (see Appendix from 2 to 6).

3. **Instrumental evaluation:**

Polysomnography: Each subject underwent a full video-polysomnographic night recording, after an adaptation night, (Morpheus – Micromed®) carried out in a standard sound-attenuated sleep laboratory, attended by technician expert in sleep assessment, after a night. The following data were included in the polysomnographic study: EEG (at least 3 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 submental muscle, EMG of bilateral tibialis anterior muscles (bipolar derivations with the two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg), and one single-lead ECG. Sleep respiratory pattern was assessed by means of nasal airflow (nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge) and oxygen saturation (pulse-oximetry) during the same night. Sleep stages, respiratory activity and legs activity were scored manually by a clinical neurophysiologist expert in sleep medicine at Sleep Disorders Center – University of Cagliari, following standard criteria[47] on 30-seconds epochs by means of the sleep analysis software SleepRT. CAP was scored manually by a neurologist expert in sleep medicine at Sleep Disorders Center – University of Parma (Italy), according to CAP scoring atlas[31].

HRV analysis: extraction of HRV features was performed by an expert engineer at the Wyss Institute for Biologically Inspired Engineering at Harvard University – Boston (MA – USA) using the commercial sotware Matlab®. Continuous single-lead ECG signals recorded simultaneously with polysomnohgraphy were employed. Before the analysis, each trace was visually evaluated in order to identify artifacts which might affect a correct analysis of HR signal, and six patients were subsequently excluded. The R peaks were detected on the ECG by means of a modified Pan-Tompkins algorithm and the R-R time series were obtained[48].

The R-R time series were divided into intervals corresponding to continuous sleep stages. Intervals corresponding to sleep stages shorter than 5 minutes or including artifacts were excluded from the analysis. For each interval the following features were computed: time-domain features, namely mean RR interval, SDNN, SDANN, SDNN index, rMSSD, pNN50%, and pNN20%; frequency-domain features, namely total power, LF, HF, LF/HF index. Features were then averaged by sleep stage (N1, N2, N3, REM and W), and in NREM light sleep (N1-N2) and in slow wave sleep (SWS or N3) prior to comparison between patients and controls.

Cardiopulmunary coupling (CPC)[32,33]: CPC analysis was performed on a continuous single-lead ECG recorded during polysomnography. Both RR and ECG-derived respiration (EDR) were extracted from the ECG, Outliers due to false or missed R-wave detections were removed. The resulting NN interval series and its associated EDR were then cubic-spline resampled at 2 Hz. The cross-spectral power and coherence of these two signals were calculated over a 1024-

sample (8.5 minutes) window using Fast Fourier Transform applied to 3 overlapping 512-sample subwindows within the 1024-sample coherence window. For each 1024-sample window the product of the coherence and cross-spectral power was computed, obtaining a spectrographic representation of cardiopulmonary coupling dynamics during sleep, as shown in the example in Fig. 1. The spectrogram shows an alternation between two distinct modes of cardiopolmonary interaction during NREM sleep: Low Frequency Coupling, LFC [0.01 Hz-0.1 Hz] and High Frequency Coupling, HFC [0.1 Hz-0.4 Hz]. During REM sleep or wakefulness, Very Low Frequency Coupling, VLFC [0 Hz-0.01] is present.

By applying thresholds to the CPC amplitude the percentage of sleep spent in LFC, HFC and VLFC modes was computed[32].

Statistical analysis: in order to assess Gaussian distribution of each parameter of both groups, the D'Agostino & Person – Normality test was performed. Data between the two groups were compared with the unpaired Student t-test in case of Gaussian distribution and with the Mann-Whitney test in case of non-parametric distribution, with significance level at $\alpha=0.05$.

RESULTS

1. **Subjects:** Among the 24 patients 5 presented bulbar onset, 1 generalized onset, 18 spinal onset), mean age was 61 years (range 26-79), mean age at onset disease was 57 years (range 25-78), with duration of disease of 4 years (range 1-10). Severity of disease, calculated with ALS-FRS (Amyotrophic Lateral Sclerosis – Functional Rating Scale)[49] (see Appendix 1) was 34.4/48 (range 12-45).

There were no differences between patients and control subjects in demographical data (age and sex). Control subjects were negative for any sleep disorders. One initially enrolled subject, did not enter the sleep study for dead.

2. **Clinical evaluation :**

   - **Sleep questionnaires: (23 patients)**

     ESS: 3 patients presented an ESS>10 (mean 5,78 ± 4,42; range 0-17).

     PSQI: mean value obtained was 8,52 ± 4,83 (range 1-18).

     BQI: 15 patients presented high risk for OSAS (obstructive sleep apnoea syndrome)

     IRLSSS: 3 patients presented RLS with severity index of 15 in two of these subjects and 19 in the other

     RBDI: 5 patients presented a score > 5

3. **Instrumental evaluation**

   Polysomnography

   - **Sleep macro-structure:** Respect to control subjects, patients presented a significant reduction of TST (p=0.0002) and sleep efficiency (p=0.0005) increase of sleep latency (p=0,264), significant increase of N1 (p=0.0001) and of WASO (p=0.0039) and a significant reduction of phase N2

(p<0.0001), of N3-SWS (p=0.0242) and of REM sleep (p<0.0001). (see table 3 for details).

- **Sleep micro-structure (CAP):** respect to control subjects, patients presented a significant reduction of CAP rate (p=0.0006) due to a marked reduction of total number of phases A (p<0.0001), with a reduction of percentage of A1, A2 and A3 phases (P<0.0001; p=0.0044; p<0.0001 respectively) and inversion of A1-A3 percentage. (see table 4 for details)

- **Sleep respiratory function:** 3 patients were excluded from analysis of respiratory function due to TST<4 hours. Among the other patients (n=20), 10 resulted to be affected by OSAS: 6 presented mild, 2 moderate, and 2 severe OSAS. 3 patients not affected by OSAS and 1 patient affected by mild OSAS presented nocturnal hypoventilation with SpO2<90% for more than 30% of TST. Mean ODI > 3% was 8,57 ± 8,86 (range 0-23,3). Mean SpO2 were: during wake 93,07 ± 2,40% (range 65-99,4); in TST 92,09 ± 2,30% (range 63,4-99,4); in NREM sleep 92,38 ± 2,37 % (range 63,4-99,2); during REM sleep 91,62 ±3,47 (range 74-99,4).

- **Sleep muscular activity:** all patients presented spontaneous muscle activity as fasciculations in almost all muscles recorded. 3 patients presented a PLM-index>15.

  HRV: respect to the control subject, ALS patients showed significant reduction in the following HRV features in frequency-domain both in sleep and in wakefulness and in parameters influenced by both sympathetic and vagal system: total power in NREM (p=0.005), LF in

NREM (p=0.01) and in REM sleep (p=0.003), HF in NREM (p=0.04) and in REM sleep (p=0.05) and in WASO (p=0.03) (see tables 5 and 6).

CPC: Patients with the most advanced pathology, i.e. those with ALS-FRS<30, had the most unstable sleep patterns, with high percentage of LFC and low percentage of HFC (<4%). Patients with the mildest pathology, i.e. those with ALS-FRS≥40, had the most stable patterns, with high percentage of HFC (>50%) and low percentage of LFC. (see Fig. 2).

DISCUSSION

The present study confirms that in ALS there is a subclinical involvement of Autonomic Nervous System, both in sympathetic and parasympathetic components. Infact respect to control subjects, patients presented a reduction of HRV features in frequency domain, influenced by both sympathetic (LF) and vagal (HF) system, and the alteration of HF was both in wakefulness and in sleep (both NREM and REM).

These findings suggest that in ALS there is an important involvement of cardiac ANS, that causes a reduction of heart reactivity to internal and external stimuli, leading to increase in mortality for sudden cardiac arrest[11,50], that it is known occur more frequently at night[11]. So, reduction of HRV in patients with ALS may represent a risk factor for sudden death during sleep. Moreover in these patients sleep structure appears to be altered, with reduction of total sleep time, reduction of sleep efficiency, reduction of N2-N3 and REM sleep, increase of sleep latency and of wake after sleep onset, and reduced CAP rate, mainly due to reduction of A1-A2 components, despite patients perceive good quality sleep, as it is evidenced from questionnaires. Reduction of CAP rate, analogously to the reduction of HRV, may reflect an alteration of cortical circuits wich underlie to the organization of sleep and autonomic functions, which are strongly interconnected[34,35,51], that in these patients seems to be characterized by a marked rigidity, with poor reactivity and reduced adaptability to external or internal stimuli.

CONCLUSION

Amyotrophic lateral sclerosis is a progressive and fatal neurodegenerative disease, and todate there are no effective therapies.

Our study confirms that in patients affected by ALS there is a subclinical involvement of autonomic nervous system and a marked alteration of sleep, confirming the evidences that ALS is not a pure motor neuron disease, but it is a multisystemic neurological syndrome.

Early detection and treatment of dysautonomia and of any sleep disorders, both sleep breathing disorders and other sleep disorders, may lead to improvement of quality of life and possibly to prolong of life expectancy.

Moreover considering the cases of sudden death during sleep, the fundamental role of sleep in homeostasis and recovery, the relashionships between disturbed sleep and cognitive deficits[52,53] in neurodegenerative diseases and the well-known association between cognitive deficits and poor prognosis in ALS[54], and the role of nocturnal hypoventilation in anticipating the respiratory failure[6], it is mandatory, during routine exams, assessing autonomic function and sleep, in order to early identify and adequately treat any disorders, with the ultimate aim of improving the quality of life and possibly prolonge life expectancy.

Figure 1: A cardio-respiratory spectrogram derived from the nocturnal ECG of a healthy subject, for whom non-REM sleep shows predominance of a stable sleep (peaks in **blue** regime), although certain time epochs present unstable sleep (peaks in **red** regime). REM, rapid eye movement sleep, and wakefulness are characterized by peaks in **green** regime.
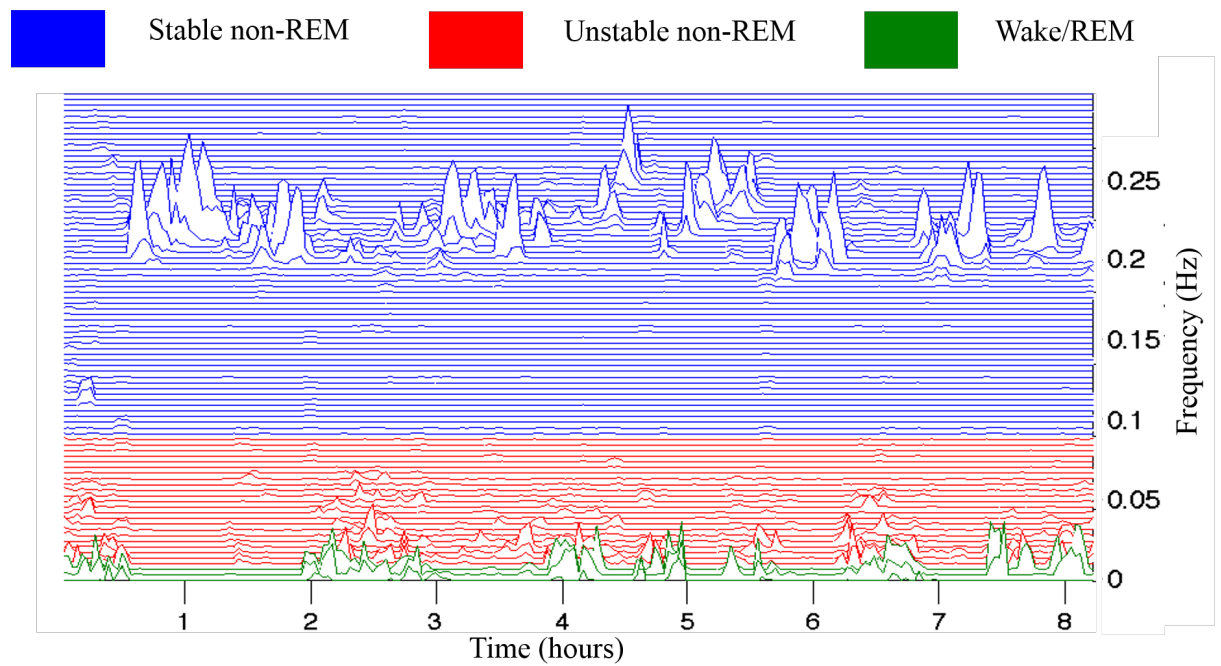
Figure 2: Cardio-respiratory spectrograms derived from the nocturnal ECG of four of hour patients. Subject 1 and subject 11, who have an advanced stage disease, present the most unstable sleep patterns, with high percentage of LFC and low percentage of HFC.

Subject 15 and subject 17, who have the mildest pathology, present the most stable patterns, with high percentage of HFC and low percentage of LFC.

Subject 1: ALS-FRS=29/48, age 74
HFC = 1.9% LFC = 67.0% Wake/REM = 25.5%

Subject 11: ALS-FRS=20/48, age 79
HFC = 3.8% LFC = 54.2% Wake/REM = 35.3%

Subject 15: ALS-FRS=40/48, age 66
HFC = 73.4% LFC = 21.9% Wake/REM = 4.7%

Subject 17: ALS-FRS=40/48, age 46
HFC = 71.9% LFC = 20.4% Wake/REM = 7.0%
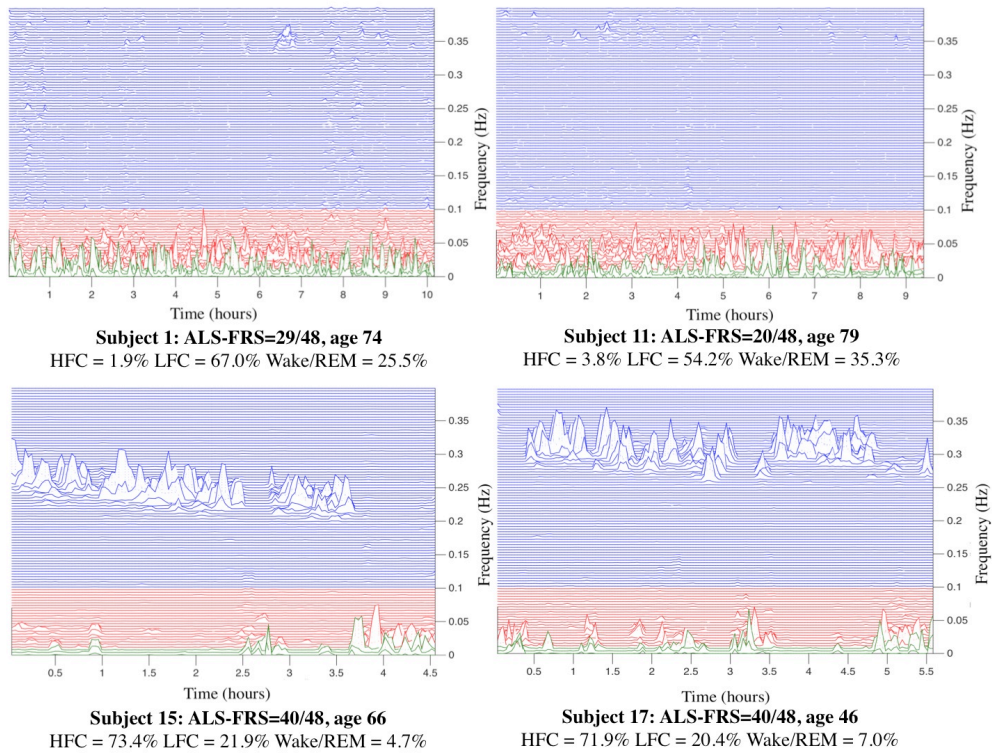
Table 1: Conventional HRV parameters in time-domain

Time-domain parameters		
Statistical		
AverageNN	ms	Average of all normal RR intervals
SDNN	ms	SD of all normal RR intervals
SDANN	ms	SD of the average normal RR inetrvals calculated over short time periods
RMSSD	ms	The square root of the mean squared differences between adjacent normal RR intervals
SDNN Index	ms	Mean of the SD of the normal RR intervals calculated over short periods time for the entire recording period
NN50		The number of pairs of adjacent normal RR intervals that differ by more than 50 ms
NN20	ms	The number of pairs of adjacent normal RR intervals that differ by more than 20 ms
PNN50	%	NN50 divided by the total number of normal RR intervals x 100
Geometrical		
HRV Triangular Index		Number of normal RR intervals divided by the height of the istogram of all the normal RR intervals measured on discrete scale with bins of 1/128 s
TINN	ms	Baseline width of the minimum square difference of triangular interpolation of the highest peak of the histogram of all normal RR intervals

Table 2: Conventional HRV parameters in frequency-domain

Frequency-domain parameters		
Total power spectrum	ms^2	Area under the entire power spectral curve, variance of all RR intervals
ULF	ms^2	Ultra low frequency power ($\leq$0.003 Hz)
VLF	ms^2	Very low frequency power (0.003-0.04 Hz)
LF	ms^2	Low frequency power (0.04-0.15 Hz)
HF	ms^2	High frequency power (0.15-0.40 Hz); (0.24-1.04 Hz) in infants and exercising adults
LFnu	nu	Normalized low frequency power (LF/(LF+HF))
HFnu	nu	Normalized high frequency power (HF/(LF+HF))
LF/HF		Ratio of the low-to high freqeuncy power

Nu: Normalized Units

Table 3: Features of sleep macrostrustructer of ALS patients and controls

Macro structure			
Feature	**Pt (mean±sd)**	**C (mean±sd)**	**pValue**
TST	321.0 ± 97.03	423.0 ± 39,64	**0.0002**
SL	35.79 ± 35.17	9.67 ± 6.68	**0.0264**
SE%	67.06 ± 16.97	87.88 ± 8.54	**0.0005**
WASO (min)	120.61 ± 67.28	49.47 ± 39.55	**0.0039**
N1 (min)	79.8 ± 39.01	27.93 ± 22.55	**0.0001**
N2 (min)	151.67 ± 51.07	228.67 ± 29.37	**< 0.0001**
N3 (min)	51.36 ± 29.12	73.87 ± 34.04	**0.0242**
R (min)	41.66 ± 26.67	93.0 ± 26.04	**< 0.0001**

Table 4: Features of sleep microstrustructer of ALS patients and controls

Micro structure			
Feature	**Pt (mean ± sd)**	**C (mean ± sd)**	**pValue**
CAP rate	30.95 ± 15.05	49.32 ± 10.20	**0.0006**
A tot (n°)	174.78 ± 106.32	341.47 ± 59.33	**< 0.0001**
A1 Index	9.95 ± 10.43	6.93 ± 8.68	**0.2322**
A1 %	25.48 ± 17.49	53.13 ± 10.99	**< 0.0001**
A2 Index	7.19 ± 5.71	74.0 ± 29.02	**< 0.0001**
A2 %	20.11 ± 8.86	31.51 ± 7.80	**0.0044**
A3 Index	17.77 ± 9.87	49.4 ± 19.77	**< 0.0001**
A3 %	54.42 ± 21.32	16.11 ± 5.98	**< 0.0001**

Table 5: p value of HRV parameters in time-domain of ALS patients and controls

Time-domain parameters							
Sleep stage	**Average NN**	**SDNN**	**SDANN**	**SDNN-I**	**RMSSD**	**pNN50**	**pNN20**
NREM sleep	0.264	**0.008**	**0.002**	**0.009**	**0.025**	**0.026**	**0.022**
REM sleep	0.526	0.231	0.622	0.180	**0.016**	**0.057**	**0.048**
WASO	0.456	0.214	0.121	0.082	0.054	0.136	0.136
N1-N2	0.238	**0.009**	**0.001**	**0.013**	**0.025**	**0.029**	**0.021**
N3	0.291	**0.029**	0.099	**0.029**	0.129	0.060	0.166
REM	0.526	0.231	0.622	0.180	**0.016**	0.057	**0.048**

Table 6: p value of HRV parameters in frequency-domain of ALS patients and controls

Frequency-domain parameters					
Sleep stages	**Total power**	**VLF**	**LF**	**HF**	**LF/HF**	**CI**
NREM sleep	**0.005**	**0.022**	**0.013**	**0.040**	0.852	0.555
REM sleep	0.231	0.481	**0.003**	**0.048**	0.622	0.071
WASO	0.192	0.385	0.062	**0.029**	0.756	0.192
N1-N2	**0.006**	**0.047**	**0.006**	**0.018**	0.950	0.231
N3	**0.029**	0.291	**0.047**	0.113	0.843	**0.029**
REM	0.231	0.481	**0.003**	**0.048**	0.622	0.231

APPENDIX 1. Scala di disabilità funzionale ALSFRS-R (ALS Functional Rating Scale – Revised)

Fonazione
4 Normale fonazione
3 Disturbo rilevabile della fonazione
2 Comprensibile con ripetizione
1 Fonazione associata a comunicazione non verbale
0 Comunicazione impossibile

Vestirsi e lavarsi
4 Normale
3 Indipendente con sforzo o con ridotta efficacia
2 Assistenza intermittente o modalità sostitutive
1 Necessità di assistenza per la cura della persona
0 Totale dipendenza

Salivazione
4 Normale
3 Lieve aumento della salivazione; può avere perdita di saliva notturna
2 Moderato eccesso di salivazione; può avere minima perdita di saliva
1 Marcato eccesso di salivazione con perdita di saliva
0 Marcata perdita di saliva; richiede uso costante del fazzoletto

Girarsi nel letto e aggiustare le lenzuola
4 Normale
3 Lento ed impacciato ma non necessita di aiuto
2 Può girarsi o aggiustare le lenzuola da solo, ma con grande difficoltà
1 Può iniziare il movimento ma non girarsi o mettere a posto le coperte da solo
0 Necessita totalmente assistenza

Deglutizione
4 Normale
3 Iniziali problemi, occasionale "strozzamento"
2 Modificazioni della consistenza della dieta
1 Necessita integrazione con sondino naso-gastrico

0 Alimentazione esclusivamente parenterale o enterale

Deambulazione
4 Normale
3 Iniziali difficoltà della deambulazione
2 Cammina con assistenza
1 Solo movimenti funzionali non deambulatori
0 Nessun movimento utile delle gambe

Calligrafia
4 Normale
3 Lento o disordinato: tutte le parole sono leggibili
2 Non tutte le parole sono leggibili
1 Capace di impugnare la penna ma non di scrivere
0 Incapace di impugnare la penna

Salire le scale
4 Normale
3 Lentamente
2 Lieve instabilità o fatica
1 Necessita assistenza
0 Non in grado

Utilizzo delle posate (alimentazione per via orale)
4 Normale
3 Rallentato ed impacciato, non necessita di aiuto
2 Può tagliare il cibo, sebbene lento ed impacciato; in alcuni casi necessita di aiuto
1 Il cibo deve essere tagliato da altri, può alimentarsi da solo lentamente
0 Deve essere imboccato

Respirazione
4 Normale
3 Dispnea quando cammina
2 Dispnea con una o più delle seguenti azioni: mangiare, lavarsi, vestirsi (ADL)
1 Dispnea a riposo, difficoltà a respirare quando si siede o si sdraia
0 Significativa difficoltà che consiglia l'uso del respiratore

Utilizzo delle posate (alimentazione per PEG)
4 Normale
3 Impacciato ma non necessita di aiuto
2 Necessita di aiuto
1 Fornisce un minimo di assistenza al personale sanitario
0 Totale dipendenza da altri

Ortopnea
4 Normale
3 Qualche difficoltà notturna con respiro più corto, non usa più di 2 compresse
2 Necessita più di due cuscini per dormire
1 Può dormire seduto
0 Incapace di dormire

Insufficienza Respiratoria
4 Normale
3 Intermittente uso di BiLevel
2 Continuo uso di Bilevel durante la notte
1 Continuo uso di Bilevel sia di notte che di giorno
0 ventilazione invasiva con intubazione o tracheostomia

APPENDIX 2. Epworth Sleepiness Scale (ESS)

Che probabilità ha di appisolarsi o di addormentarsi nelle seguenti situazioni, indipendentemente dalla sensazione di stanchezza?

La domanda si riferisce alle usuali abitudini di vita nell'ultimo periodo.
Qualora non si sia trovato di recente in alcune delle situazioni elencate sotto, provi ad immaginare come si sentirebbe.

Usi la seguente scala per scegliere il punteggio più adatto ad ogni situazione:
O = non mi addormento mai
1 = ho qualche probabilità di addormentarmi
2 = ho una discreta probabilità di addormentarmi
3 = ho un'alta probabilità di addormentarmi

Situazioni:

a. Seduto mentre leggo |____|

b. Guardando la TV |____|

c. Seduto, inattivo in un luogo pubblico (a teatro, ad una conferenza) |____|

d. Passeggero in automobile, per un'ora senza sosta |____|

e. Sdraiato per riposare nel pomeriggio, quando ne ho l'occasione |____|

f. Seduto mentre parlo con qualcuno. |____|

g. Seduto tranquillamente dopo pranzo, senza avere bevuto alcoolici |____|

h. In automobile, fermo per pochi minuti nel traffico |____|

SOMMA |____|

RISULTATO

Se il punteggio totalizzato è superiore a 10 ciò è indicativo di una sonnolenza diurna eccessiva.

APPENDIX 3. INDICE DI QUALITA' DEL SONNO DI PITTSBURGH (PSQI)

1. Nel mese passato a quale ora vi siete di solito coricati?

2. Nel mese passato, quanto tempo (in minuti) avete impiegato mediamente ad addormentarvi ogni sera?

3. Nel mese passato a che ora vi siete alzato abitualmente?

4. Nel mese passato quante ore di sonno effettivo ha avuto ogni notte?

5. Nel mese passato quante volte volte ha avuto problemi di sonno per ciascuno dei seguenti motivi?

• Non vi siete potuti addormentare entro 30 minuti:

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Vi siete svegliati nel mezzo della notte o al mattino presto

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete dovuto fare uso del bagno

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Non avete potuto respirare correttamente

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete tossito o russato rumorosamente

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete avvertito troppo freddo

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete avvertito troppo caldo

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete fatto brutti sogni

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Avete avuto dolori

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Per altri motivi (descriveteli)

Quante volte nell'ultimo mese non avete dormito bene a causa del suddetto motivo

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

6. Nell'ultimo mese come valutate globalmente la qualità del vostro sonno?

molto buona abbastanza buona abbastanza cattiva molto cattiva

7. Nell'ultimo mese quante volte avete assunto farmaci per dormire (prescritti dal medico o comunque ottenuti)?

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

8. Nell'ultimo mese quante volte avete avuto difficoltà a restare svegli durante la guida, il pasto, un'attività sociale?

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

9. Nel mese passato, in che misura ha rappresentato per voi un problema avere abbastanza antusiasmo per fare ciò che dovevate fare?

Nessun problema un piccolo problema un certo problema un problema grosso

10. Avete un partner di letto o condividete la camera da letto con qualcuno?

No il partner in un'altra camera stessa camera diverso letto stesso letto

11. Se avete un partner o un compagno di camera domandategli quante volte nell'ultimo mese avete presentato:

• Un forte russamento

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Lunghe pause respiratorie durante il sonno

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Movimenti o scosse delle gambe durante il sonno

mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

• Episodi di confusione o disorientamento durante il sonno
mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett
• Altri motivi di agitazione durante il sonno:
Li descriva:
mai meno di 1 volta/sett 1-2 volte/sett 3 o + volte/sett

CALCOLO DEL PUNTEGGIO:

Componente 1. Qualità soggettiva del sonno
• **Domanda 6:** molto buona = 0; abbastanza buona = 1; abbastanza cattiva = 2; molto cattiva = 3.
Punteggio: ___
Componente 2. Latenza del sonno
• **Domanda 2:** <15 min: 0; 16-30 min: 1; 31-60 min: 2; >60min: 3
punteggio___
• **Domanda 5a:** mai = 0; meno di 1 volta/sett = 1; 1-2 volte/sett = 2; 3 o + volte/sett = 3
Punteggio___
• Somma domanda 2 + domanda5a: 0 = 0; 1-2 = 1; 3-4 = 2; 5-6 = 3
Punteggio:___
Componente 3: durata del sonno
• **Domanda 4:** >7 ore = 0; 6-7 ore = 1; 5-6 ore = 2; <5 ore = 3
Punteggio___
Componente 4: efficienza abituale del sonno
• n° di ore dormite (domanda 4): ___
• n° di ore trascorse a letto (vd. Domande 1 e 3):___
• calcolare l'efficienza del sonno in percentuale: (n° ore dormite/n° ore trascorse a letto) x 100
• attribuire il punteggio come segue: >85% = 0; 75-84% = 1; 65-74%= 2; < 65% = 3
Punteggio ___
Componente 5: disturbi del sonno
• esaminare le domande dalla 5b alla 5l e attribuire il punteggio per ogni domanda come segue:
mai = 0; < 1 volta/sett = ; 1-2 volte /sett = 2; 3 o + volte/sett = 3
• addizionare i punteggi da 5b a 5l
• attribuire il punteggio come segue: 0 = 0; 1-9 = 1; 10-18 = 2; 19-27 = 3.
Punteggio___
Componente 6: utilizzo di un farmaco per dormire
• esaminare la domanda 7: mai = 0; <1 volta/sett = 1; 1-2 volte/sett = 2; 3 o + volte/sett = 3.
Punteggio___
Componente 7: cattivo stato di forma durante la giornata
• esaminare la domanda 8: mai = 0; <1 volta/sett = 1; 1-2 volte/sett = 2; 3 o + volte/sett = 3. ____
• esaminare la domanda 9: nessun problema = 0; piccolo problema = 1; un certo problema = 2;
problema grosso = 3. ___
• addizionare i punteggi delle domande 8 e 9: ___
• attribuite il punteggio come segue (somma di 8 e 9): 0 = 0; 1-2 = 1; 3-4 = 2; 5-6 = 3
Punteggio ____

Punteggio globale (somma delle 7 componenti): ____

Più il punteggio è vicino a 21 tanto più la qualità del sonno è scarsa

APPENDIX 4. **Questionario di screening per il Disturbo del Comportamento in sonno REM (RBD)**

1. mi capita talvolta di fare sogni vividi (a contenuto intenso, con forte carica emotiva)
SI \ NO

2. i miei sogni hanno spesso contenuto aggressivo SI \ NO

3. il contenuto dei miei sogni spesso correla con il mio comportamento nel sonno SI \ NO

4. so di muovere le braccia e\o le gambe nel sonno SI \ NO

5. mi capita talvolta nella concitazione del sogno, di colpire il partner o di farmi male
SI \ NO

6. ho, oppure ho presento i seguenti fenomeni in sonno:

- parlare, gridare, imprecare o ridere forte SI \ NO

- fare rapidi movimenti delle gambe come calciare SI \ NO

- fare movimenti complessi o gesti che sono inusuali durante il sonno

come ondeggiare, salutare, catturare zanzare, cadere dal letto SI \ NO

- ritrovare oggetti caduti intorno al letto come la lampada, libri, occhiali etc SI \ NO

7. mi capita che i miei movimenti mi sveglino SI \ NO

8. al risveglio spesso ricordo chiaramente il contenuto dei miei sogni SI \ NO

9. il mio sonno è frequentemente disturbato SI \ NO

10. ho o ho avuto una patologia neurologica tra queste: ictus, trauma, parkinsonismo,
RLS, narcolessia, depressione, epilessia, malattia infiammatoria del SNC? SI \ NO
Quale?
Totale SI___

Se il punteggio è superiore a 5 si pone il sospetto di RBD si consiglia Video-Polisonnografia

APPENDIX 5. Questionario di Berlino (**)

SCEGLIERE LA RISPOSTA GIUSTA AD OGNI DOMANDA

CATEGORIA 1

1.   Siete solito russare?
_A. Sì
_B. No
_C. Non so

2.   Se russa: il suo russare è:
_A. Leggermente più forte della respirazione
_B. Più forte di chi parla
_C. Più forte del parlare
_D. Molto alto – può essere ascoltata in stanze adiacenti

3.   Le capita di russare:
_A. Quasi ogni giorno
_B. 3-4 volte a settimana
_C. 1-2 volte a settimana
_D. 1-2 volte al mese
_E. Mai o quasi mai

4.   Il suo russare ha mai interessato altre persone?
_A. Sì
_B. No
_C. Non so

5.   Qualcuno ha notato che interrompe la respirazione durante il sonno?
_A. Quasi ogni giorno
_B. 3-4 volte a settimana
_C. 1-2 volte a settimana
_D. 1-2 volte al mese
_E. Mai o quasi mai

CATEGORIA 2

6.   Quante volte si sente stanco o affaticato dopo il sonno notturno?
_A. Quasi ogni giorno
_B. 3-4 volte a settimana
_C. 1-2 volte a settimana
_D. 1-2 volte al mese
_E. Mai o quasi mai

7.   Durante il giorno si sente stanco, affaticato o svogliato?
_A. Quasi ogni giorno
_B. 3-4 volte a settimana
_C. 1-2 volte a settimana
_D. 1-2 volte al mese
_E. Mai o quasi mai

8. Si è mai appisplato o addormentato durante la guida di un veicolo?
_A. Sì
_B. No

In caso affermativo:

9. Con quale frequenza si verifica il problema?
_A. Quasi ogni giorno
_B. 3-4 volte a settimana
_C. 1-2 volte a settimana
_D. 1-2 volte al mese
_E. Mai o quasi mai

CATEGORIA 3

10. Ha la pressione alta? Calcolare il BMI (Body Mass Index*)
_ Sì
_ No
_ Non so

Body Mass Index = peso/altezza^2   Es. $\dfrac{\text{Kg. }80}{\text{m }1.80} = \dfrac{80}{3.24} = 24{,}69$ (B.M.I.)

** Nikolaus C. Netzer, MD; Riccardo A. Stoohs, MD; Cordula M. Netzer; Kathryn Clark; and Kingman P. Strohl, MD.: Using the Berlin Questionnaire To Identify Patients at Risk for the Sleep Apnea Syndrome. ANN INTERN MED. 5 October 1999;131(7):485-491.
** Gross JB, Bachenberg KL, Benumof JL, Caplan RA, Connis RT, Cote CJ, Nickinovich DG, Prachand V, Ward DS, Weaver EM, Ydens L, Yu S: Practice guidelines for the perioperative management of patients with obstructive sleep apnea: A report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. ANESTHESIOLOGY 2006; 104:1081–93

<div align="center">

PUNTEGGI QUESTIONARIO DI BERLINO

</div>

Tratto da: NC Netzer, Stoohs RA, CM Netzer, Clark K, Strohl KP). Utilizzo del questionario di Berlino per identificare i pazienti a rischio per la sindrome delle apnee notturne. Tabella 2 - Ann Intern Med. 5 ottobre 1999; 131 (7) :485-91.

Il questionario si compone di 3 categorie relative al rischio di apnea del sonno. I pazienti possono essere classificati ad alto rischio o basso rischio, sulla base delle loro risposte ai singoli elementi e con la valutazione complessiva nelle categorie sintomo.

Categorie e punteggio:
Categoria 1: punti 1, 2, 3, 4, 5.
Punto 1: se 'Sì', assegnare 1 punto
Punto 2: se 'c' o 'd' è la risposta, assegnare 1 punto
Punto 3: se 'a' o 'b' è la risposta, assegnare 1 punto
Punto 4: se 'a' è la risposta, assegnare 1 punto
Punto 5: se 'a' o 'b' è la risposta, assegnare 2 punti
Categoria 1 è positivo se il punteggio totale è di 2 o più punti

Categoria 2: articoli 6, 7, 8 (il punto 9 va osservato separatamente).
Punto 6: se 'a' o 'b' è la risposta, assegnare 1 punto
Punto 7: se 'a' o 'b' è la risposta, assegnare 1 punto
Punto 8: se 'a' è la risposta, assegnare 1 punto
Categoria 2 è positivo se il punteggio totale è di 2 o più punti

Categoria 3 è positivo se la risposta al punto 10 è Sì
(se il Body Mass Index del paziente è maggiore di 30kg/m2. (il BMI deve essere calcolato; è definito come peso (kg) diviso altezza (m) al quadrato, vale a dire, kg/m2).
Ad alto rischio OSAS: 2 o più categorie positive
Basso rischio OSAS: 1 o nessuna categoria considerata positiva

APPENDIX 6. Scala di valutazione della severità della RLS

1. come giudica il Suo disagio\dolore alle gambe o agli arti?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

2. come valuta la necessità di muovere gli arti?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

3. che sollievo rileva rispetto al disagio prodotto dalla RLS con il movimento?
(4) nessun sollievo
(3) lieve sollievo
(2) Moderato
(l) totale
(0) nessun disturbo RLS

4. quale è il grado di compromissione del Suo sonno a seguito del disagio RLS?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

5. quale è il grado di stanchezza o la sonnolenza conseguente?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

6. nel complesso come giudica la gravità dei suoi disturbi alle gambe?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

7. che frequenza hanno i disturbi alle gambe?
(4) Molto grave (6-7 giorni su sette)
(3) Grave (4-5 giorni su 7)
(2) Moderato (2-3 giorni su 7)
(l) Lieve (1 giorno su 7)
(0) nessuno

8. come giudica la severità del disturbo nell'arco della giornata?
(4) Molto grave (8 ore in media)
(3) Grave (da 3 a 8 ore)
(2) Moderato (1-3 ore)
(l) Lieve (meno di 1 ora)
(0) nessuno

9. come giudica l'impatto del disturbo alle gambe nella vita quotidiana e di relazione?
(4) Molto grave

(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno
10. in che modo il disturbo incide sul suo umore determinando ansia, depressione, irritabilità etc.?
(4) Molto grave
(3) Grave
(2) Moderato
(l) Lieve
(0) nessuno

Punteggio:
Molto grave 31-40 unti
Grave 21-30
Moderato 11-20
Lieve 1-10
Nessuno 0

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