Polysomnography Test and Sleep Disordered Breathing in Prader-Willi Syndrome

ANDREEA- IULIA DOBRESCU[1], LAVINIA ARDELEAN[3], CLARA MATEI[4], MIRCEA TAMPA[4], MARIA PUIU[1*], STEFAN MIHAICUSA[2]

[1] "Victor Babes" University of Medicine and Pharmacy Timisoara, Genetics Discipline, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[2] Victor Babes" University of Medicine and Pharmacy, Timisoara, Department of Pneumology, 2 E. Murgu Square, 300041 Timisoara, România

[3] Victor Babes" University of Medicine and Pharmacy, Timisoara, Department 1, Tehnology of Dental Materials and Devices in Dental Medicine,2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[4] "Carol Davila" University of Medicine and Pharmacy, 8 Eroii Sanitari Blv., 060474, Bucharest, Romania

Polysomnography is a new and innovative test used for the diagnosis of sleep disorders. It offers the possibility to identify and to early treat important diseases which can lead sudden to death in children and adults too. The portable monitor simplifies the procedure and it permits to monitor the patients at home. Obesity is the most powerful and the only reversible risk factor for obstructive sleep apnea. This condition is one of the most serious problem of the 21st century. It can appear like common obesity caused by an increased food intake and it is also part of some rare genetic syndromes. Prader Willi Syndrome is a genetic disorder caused by an abnormality on the 15th chromosome. It is the most common known genetic cause of life-threatening obesity in children. The study aims to describe sleep disorders in patients diagnosticated with this genetical syndrome. The evaluated patients associated a characteristically phenotype for Prader Willi Syndrome with unrest sleep and they had no treatment before. A high number of obstructive sleep apneas and rapid eye movement sleep alteration was registered. Breath and cardio-vascular pathological changes were also identified. Large fluctuations in heart rate and relatively long duration of low oxygen saturation was threatening patients life and nasal continuous airway pressure was needed in order to reverse respiratory and cardiovascular symptoms.

Keywords: polysomnography, obstructive sleep apnea, sleep disorders, Prader Willi Syndrome

Polysomnography (PSG) is a new and innovative test used for the diagnosis of any sleep disorders. PSG can directly monitor and quantify the number of respiratory events (obstructive, central, or complex) and the resultant hypoxemia and arousals related to the respiratory events or even independent of the respiratory events [1]. It is a multi-parametric test, a comprehensive recording of the biopsychological changes that occur during sleep. There are different types of PSG which offer information about many body functions. They can present the brain activity (by electroencephalography- EEG), eye movements (by electrooculography- EOG), muscle activity or skeletal muscle activation (by electromyography- EMG) and heart rhythm (by electrocardiography - ECG), ventilatory variables (movement of chest wall and airflow at mouth and nose level), arterial oxygen saturation (by finger/ear pulse oximetry). Supplementary, the devices can record sounds to measure snoring or they can monitor the body temperature, incident light intensity, penile tumescence or pressure and pH at various esophageal levels . The most accessible type of PSG is the portable monitoring (PM), an indicated procedure for the patients for whom laboratory PSG is not possible by different reasons (immobility, critical state, flawed collaboration). The PM is also indicated to monitor the non- nasal continuous airway pressure (nCPAP) treatments of sleep apnea including oral appliances, weight loss, and upper airway surgery. In 2008, Medicare approved the use of unattended home sleep monitoring devices if the patient received a complete clinical evaluation and does not have atypical or complicated symptoms and the studies were read by a trained sleep specialist [2,3]. Center for Medicare & Medicaid Services guidelines divided the portable monitors according with the total number of evaluated functions.

Type I evaluates the following channels: EEG, EOG, ECG/ Heart rate, Chin EMG, Limb EMG, respiratory effort at thorax and abdomen, air flow from nasal canula thermistor and/ or X-Flow (AASM recommends RIP technology, pulse oximetry , additional channels for CPAP/BiPap levels, CO_2,, *p*H pressure.

Type II monitors a minimum of 7 channels (EEG, EOG, EMG, ECG-heart rate, airflow, respiratory effort, oxygen saturation.

Type III evaluates a minimum of 4 channels, including ventilation or airflow (at least 2 channels of respiratory movement or airflow), heart rate or ECG, and oxygen saturation.

Type IV does not meet requirements for other types, and many measure only 1-2 parameters (oxygen saturation or airflow).

The recommendations for the use of portable monitors are very clear [4]:

- PM for the diagnosis of Obstructive Sleep Apnea (OSA) should be performed only in conjunction with a comprehensive sleep evaluation. Clinical sleep evaluations using PM must be supervised by a practitioner with board certification in sleep medicine or an individual who fulfills the eligibility criteria for the sleep medicine certification examination. In the absence of a comprehensive sleep evaluation, there is no indication for the use of PM.

- Provided that the recommendations of 1.1 have been satisfied, PM may be used as an alternative to PSG for the

* *email: maria_puiu@umft.ro; Tel: 0040745138917*

diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA. PM should not be used in the patient groups described below (those with comorbidities, other sleep disorders or for screening).

- PM is not appropriate for the diagnosis of OSA in patients with significant comorbid medical conditions that may degrade the accuracy of PM, including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease or congestive heart failure.

- PM is not appropriate for the diagnostic evaluation of OSA in patients suspected of having other sleep disorders, including central sleep apnea, periodic limb movement disorder (PLMD), insomnia, parasomnias, circadian rhythm disorders or narcolepsy.

- PM is not appropriate for general screening of asymptomatic populations.

- PM may be indicated for the diagnosis of OSA in patients for whom in-laboratory PSG is not possible by virtue of immobility, safety or critical illness.

- PM may be indicated to monitor the response to nCPAP treatments for obstructive sleep apnea, including oral appliances, upper airway surgery and weight loss.

At a minimum, the PMs must record airflow, respiratory effort and blood oxygenation. The type of biosensors used to monitor these parameters for in-laboratory PSG are recommended for use in PMs. In order to detect apnea an oronasal thermal sensor is used and to detect hypopnea a nasal pressure transducer is used. Ideally, PMs should use both sensor types.

Sleep apnea is represented by recurrent episodes of partial (hypopnea) or complete (apnea) obstruction of the upper airways that last for at least 10 s [5] with desaturation of 2-4%, often accompanied by excessive daytime sleepiness, impaired cognitive function and increased cardiovascular risk. It frequently leads to sudden death [6,7]. Apneas are classified into central sleep apnea (neural drive to all respiratory muscles is abolished [8]), OSA (airflow ceases despite continuing respiratory drive because of occlusion of the oropharyngeal airway), mixed apnea and hypopnea (50% reduction of airflow lasting at least 10 s).

The American Academy of Sleep Medicine published in 2007 the standardized criteria for the staging of sleep [9].

OSA is the most common type of sleep-disordered breathing. In literature, snoring is considered the initial symptom in sleep disorders and it increases in association with medical disorders that may serve to exacerbate the disorder [9]. OSA is frequently involved in sudden death in children and adults. The most significant risk is for the patients with obesity because of low muscle tone and soft tissue around the airway.

Prader-Willi syndrome (PWS) is the most common known genetic cause of life-threatening obesity in children. The most important feature of PWS is the absence of satiety and the occurrence of morbid obesity. Patients have also morphological characteristics [1] that may lead to the occurrence of sleep apnea: typical facial features and hypotonia [10,11].

Experimental part

Materials and methods

Four patients with PWS were evaluated, aged between 6 and 24 years, 1 male and 3 females. Clinically, they

EEG background	Alpha EEG: - Frequency of 8-13 Hz - Produced in occipital region - Crescendo-decrescendo appearance	Theta EEG: - Frequency of 3-7 Hz - Produced in the central vertex region - No amplitude criteria - Most common sleep frequency	Delta EEG: - EEG frequency of 0.5-2 Hz - Seen predominantly in frontal region - Amplitude of greater than 75 microvolts
Sleep spindle	- Frequency of 12-14 Hz - Produced in central-vertex region - Greater than 0.5-3 seconds in duration 0.5-second spindles with 6-7 cycles - Indicative of stage 2 sleep		
K complexes	- Sharp, slow waves with a negative, then positive, deflection - No amplitude criteria - Duration must be at least 0.5 seconds - Predominantly produced in central-vertex region - Indicative of stage 2 sleep - May occur with or without stimuli		
Wake stage	- Greater than 50% of each epoch contains alpha activity - Eye blinks at a frequency of 0.5-2 Hz - Reading eye movements - Irregular conjugate rapid eye movements associated with normal or high chin tone.		
Stage N1 (formerly stage 1)	- Greater than 50% of the epoch contains theta activity (4-7 Hz) with slowing of the background rhythms greater than or equal to 1 Hz from those of stage wake - Vertex sharp waves - Slow-rolling eye movements in EOG channels - Relatively high submental EMG tone		
Stage N2 (formerly stage 2)	- Theta activity (4-7 Hz) - K-complexes and sleep spindles occur episodically		
	- High tonic submental EMG		

Table 1
STAGING OF SLEEP

Stage N3	- Greater than 20% of each epoch must contain delta activity - Amplitude of 75 microvolts or greater - Submental muscle tone may be slightly reduced		
Discontinued former stage 3	- Between 20-50% of each epoch must contain delta activity - Amplitude of 75 microvolts or greater - Submental muscle tone may be slightly reduced		
Discontinued former stage 4	- Greater than 50% of the epoch has scorable delta activity - Amplitude of 75 microvolts or greater - Submental EMG activity slightly reduced from that of light sleep		
REM sleep	- Rapid eye movements - Low amplitude, mixed frequency EEG (similar to awake pattern) - Atonia or the lowest tonic submental EMG - May see saw-tooth waves		

presented typical PWS phenotype. They also associate restless sleep with daytime sleepiness. All patients underwent a complete physical examination and they were also asked about concurrent symptoms, respiratory, digestive, nephrological or any other symptoms or pain. One of the evaluated patients was a 21 years old female, 150 cm/105 kg, body mass index (BMI) 46.66 kg/m2, neck circumference 39 cm, abdominal circumference 121 cm, hip circumference 141 cm, blood pressure 120/70 mmHg, reported apneas, no snoring, Epworth Sleepiness Scale 3 (a scale used to appreciate daytime sleepiness using a very short questionnaire), no excessive daytime somnolence, seldom morning headache, disturbed sleep, nicturia, 2-3 awakenings, normal uvula, tonsils, septum, Mallampati Score (a score used to evaluate the risk of sleep apnea) III - soft and hard palate and base of the uvula are visible , treated with Levothyroxine (hypothyroidism).

To diagnose sleep apnea, we have been used a PM type III [18]. Apnea was defined by an 80% or greater reduction in the airflow signal with persistent respiratory effort lasting 10 seconds or longer. Hypopnea was defined as a 30% or greater reduction in the airflow signal with persistent respiratory effort lasting at least 10 s associated with a desaturation of 4% or greater. OSA syndrome degree was determined by the apnea/hypopnea index (AHI) defined as the total number of obstructive apneas and hypopneas per hour of sleep. Absence of OSA or mild, moderate and severe degrees were defined by an AHI of $\leq$ 4.9, 5-14.9, 15-29.9, and $\geq$ 30 events/hour, respectively. Mean desaturation and desaturation index were measured with the incorporated finger pulse oxymeter.

Ethical issues

We obtained the written informed consent after discussion with each parent about the suspected diagnostic, the nature and purpose of the proposed procedures and evaluations, the risks and benefits of procedures, alternatives. A detailed explanation of the study protocol was provided in order to obtain the acceptance of referral physicians. The study procedures were standardized and noninvasive. We did not performed any unusefull investigation for the patients. Study visits did not add any additional effort or supplemental budget for the clinic. We have always respected the confidentiality of the patients data.

Results and discussions

The shortest recording had TIB (time in bed) 438 minutes and the longest one had 546 min (table 2).

PSG: TIB 523 min, sleep period time (SPT) 488.5 min, wake before sleep 32 min, wake during sleep 19,5 min , sleep onset 32 min, total sleep time (TST) 469 min, R (REM) 55 min, N (Non REM) duration 416 min, slow wave sleep (SWS) duration 78.5 min, sleep efficiency N1 (100 x TST/TIB) 89.7%, sleep efficiency N2 (100 x TST/SPT) 96%, sleep efficiency N3 (N3+ REM/TST) 28.5% (table 2), AHI 54.8/h, central 0.5/h (mean duration MD 13.4 s), obstructive 6/h (MD 12 s) , mixed 0,1/h (MD 12 s), hypopnea AHI 48.1/h (MD 16 s), periodic breathing total duration 1.57 min (0.3% of sleep), central apnea total duration 1.68 min (0.3% of sleep). Mean heart rate (HR) 88.6 ±6.89 beats per minute

Table 2

SLEEP RECORDING TIB (WITH TIME IN BED), SPT (SLEEP PERIOD TIME), TST (TOTAL SLEEP TIME), WK (WAKE), TWK (TOTAL WAKE DURATION), REM (RAPID EYE MOVEMENT), NREM (NON RAPID EYE MOVEMENT), SWS (SLOW WAVE SLEEP)

Recording duration	523.0min	Recording start -> end
TIB	523.0min	Light off -> Light on
SPT	488.5min	Sleep Onset -> Last Sleep Page
TST	469.0min	REM + NREM + MVT (during SPT)
WK before sleep	32.0 min	WK from Light off to Sleep onset
WK during sleep	19.5 min	SPT - TST
WK after sleep	0.0 min	WK from Last sleep page to Light on
TWK duration (tot)	51.5 min	All WK summed
REM duration	55.0 min	REM (during TIB)
NREM duration	416.0min	S1 + S2 + S3 + S4 (during TIB)
SWS duration	78.5 min	S3 + S4 (during TIB)
Movement	0.5 min	MVT (during TIB)

Table 3
SLEEP EFFICIENCY

Sleep efficiency 1	89.7%	100 x TST/TIB
Sleep efficiency 2	96.0%	100 x TST/SPT
Sleep efficiency 3	28.5%	100 x (N3+REM)/TST
Inter-sleep WK	4.0%	WK in sleep / SPT

Table 4
RESPIRATORY EVENTS: CA- CENTRAL APNEA, OA – OBSTRUCTIVE APNEA, MA- MIXED APNEA, Sum Ap – SUM OF APNEAS, HYP- HYPOPNEA, EVENTS, INDEX – NUMBER OF EVENTS PER HOUR OF SLEEP

	CA	OA	MA	Sum Ap	Hyp	Events
Settings (sec)	10.0	10.0	10.0	-	10.0	-
Number	4	47	1	52	376	428
Max (sec)	15.5	22,5	12.0	22.5	53.0	53.0
Mean (sec)	13.4	12.0	12.0	12.1	16.0	15.5
Tot duration (min)	0.9	9.4	0.2	10.5	100.0	110.5
TST (469.0 min)						
% of TST	0.2	2.0	0.0	2.2	21.3	23.6
Index [#/h TST]	0.5	6.0	0.1	6.7	48.1	54.8

(BPM), average oxygen saturation 96%, desaturation index 27,2/h, maxim desaturation 45 s, mean of the respiratory event SpO2 min levels 93%, mean of the respiratory event SpO2 min levels with desaturation 92%, minimum of the respiratory event SpO2 min levels 79%, lowest SpO2 ($\geq$ 2 s) 79%, arousal index 5,8/h sleep.

We registered obstructive, central and mixed apnea, hypopnea and short wakes caused by respiratory events (table 4, fig. 3) in variable number and durations.

In the present study, we evaluated sleep and sleep related breathing patterns in a group of patients with PWS. All patients were suffering of sleep apnea, defined as AHI > 1. Our findings are consistent with previously reported studies. In literature, several studies investigated the nature and the presence of sleep disorders in PWS. The researchers found the same sleep breathing events like we recorded at our patients [12,13].

OSA is a highly prevalent disorder affecting 2–4% of the adult population.

The condition occurs due to repetitive collapse of the upper airway during sleep, leading to markedly reduced (hypopnea) or absent (apnea) airflow. The patient makes progressively larger respiratory efforts to re-establish airflow in the collapsed airway during an obstructive apnea, until there is arousal from sleep and resumption of breathing. Repetitive arousals from sleep result in sleep fragmentation, impairments in sleep architecture and a marked reduction in rapid eye movement and slow-wave sleep.

Daytime sleepness was associated with higher AHI, low SaO2 level and higher BMI. They also found that higher impulsivity was associated with lower minimum SaO2, an increased arousal index and higher BMI [14]. We found some studies who identified REM abnormalities and described a relation between them and narcolepsy-like syndrome. We did not find this kind of symptoms (cataplexy, hypnagogic/ hypnopompic hallucinations, and sleep paralysis) at our patients [15]. Asymptomatic patients with PWS should be evaluated for sleep disorders at a sufficiently young age, before the development of the syndrome.

In literature it is stated that growth hormone therapy has a positive effect regarding sleep disorders.

The 4 patients we evaluated needed nCPAP in sleep. Weight loss can also help these patients to breathe better. Our results are similarly with literature results [16,17].

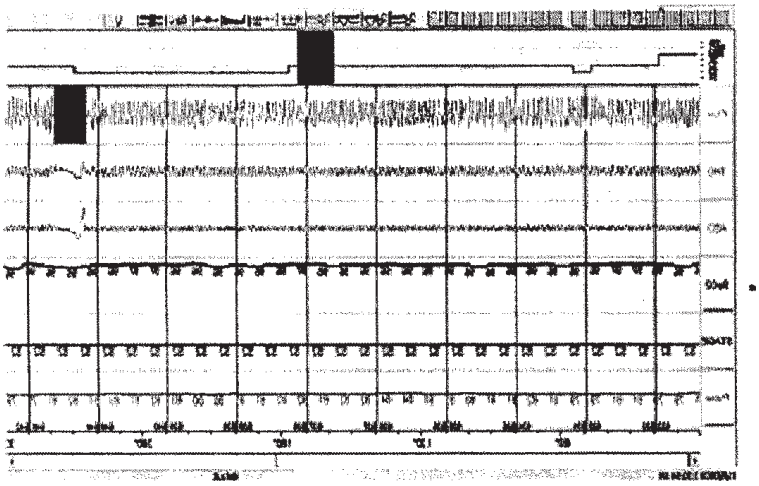

Fig.1. PSG registration, epoc of 5 min. Flow: nasal flow. THO: thoracic movements. ABD: abdominal movements. SpO2: oxygen saturation. STAGE: S2 or N2 of sleep. Central event: no flow, lack of thoracic and abdominal movements.

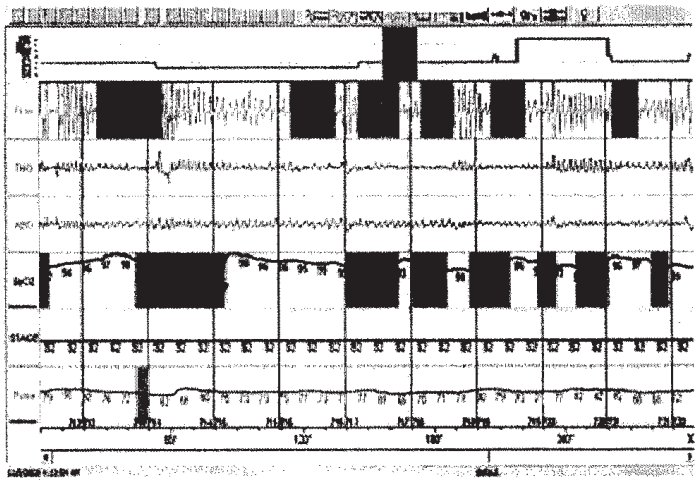

Fig. 2. PSG registration, epoc of 5 min. Flow: nasal flow. THO: thoracic movements. ABD: abdominal movements. SpO2: oxygen saturation. STAGE: S2 or N2 of sleep. HYP: hypopnea, reduced flow, thoracic and abdominal movements. Multiple apneas and hypopneas, severe repeated desaturations, heart rhythm variability

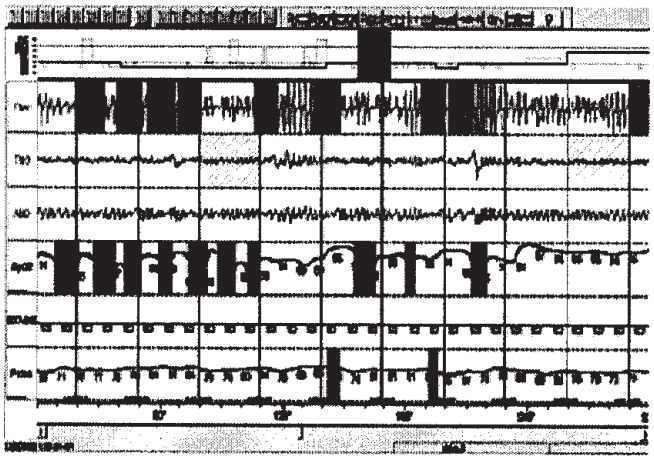

Fig. 3. PSG registration, epoc of 5 minutes. Flow: nasal flow. THO: thoracic movements. ABD: abdominal movements. SpO2: oxygen saturation. STAGE: S2 or N2 of sleep. Multiple apnea events with repeated severe desaturations and increased heart rate variability.

Conclusions

All our patients had sleep disorders: 2 forms of severe OSA and 2 had moderate form. They also associated breath difficulties and low SaO2 with large heart rate variations. Those symptoms were affecting their sleep and were threatening their life. The PM was a very efficient method to evaluate the sleep disorders in those patients with a rare genetic disease. Even if the patients had a low intelligent level, the accessibility of the procedure gave us the possibility to early diagnose and offer an efficient treatment for those dangerous diseases. It is important for both physicians and patients to keep in mind all the additional factors that affect the sleep architecture, especially the used drugs. The sleep disorders of PWS patients represent a challenge for physicians and for researchers too and new complex studies with more evaluated body functions are necessary.

References

1. BLOCH KE. Polysomnography: a systematic review. Technol Health Care. Oct 1997;5(4):285-305.

2. CAMPBELL AJ, NEILL AM. Home set-up polysomnography in the assessment of suspected obstructive sleep apnea. J Sleep Res. Mar 2011;20(1 Pt 2):207-13.

3. AYAS NT, FOX J, EPSTEIN L, RYAN CF, FLEETHAM JA. Initial use of portable monitoring versus polysomnography to confirm obstructive sleep apnea in symptomatic patients: an economic decision model. Sleep Med. Mar 2010;11(3):320-4.

4. *** Journal of Clinical Sleep Medicine, Vol. 3, No. 7, 2007, Recommendations

5. *** American Academy of Sleep Medicine. International Classification of Sleep Disorders. In: Diagnostic and Coding Manual. Second Edition. Westchester, Ill: American Academy of Sleep Medicine; 2005.

6. NIETO FJ, YOUNG TB, LIND BK, SHAHAR E, SAMET JM, REDLINE S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. Apr 12 2000.

7. JAVAHERI S, PARKER TJ, LIMING JD, CORBETT WS, NISHIYAMA H, WEXLER L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation. Jun 2 1998.

8. BLOCH KE. Polysomnography: a systematic review. Technol Health Care. Oct 1997;5(4):285-305

9.IBER, C; ANCOLI-ISRAEL, S; CHESSON, A; QUAN, SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine. Westchester: 2007

10. DAVIES RJ, ALI NJ, STRADLING JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnea syndrome. Thorax. Feb 1992.

11. ROWLEY JA, ABOUSSOUAN LS, BADR MS. The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. Sleep. Nov 1 2000.

12. BLOCH KE. Polysomnography: a systematic review. Technol Health Care. Oct 1997;5(4):285-305

13. TICE JA. Portable devices used for home testing in obstructive sleep apnea.

14. *** Dietrich B. Polysomnography in drug development. J Clin Pharmacol. Jan 1997

15. NIXON GM, BROUILLETTE RT. Sleep and breathing in Prader-Willi syndrome. Pediatr Pulmonol. 2002;34(3):209–17.

16.HELBING-ZWANENBURG B, KAMPHUISEN HA, MOURTAZAEV MS. The origin of excessive daytime sleepiness in the Prader-Willi syndrome. J Intellect Disabil Res. 1993;37(6):533–41.

17. *** Centers for Medicare & Medicaid Services (CMS). Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) .

18. FISHER J , DOGAS Z , BASETTI CL , BERG S , GROTE L , JENNUM P , LEVY P, MIHAICUTA S, NOBILI L , RIEMANN D , PUERTAS CUESTA FJ , RASCHKE F , SKENE DJ, STANLEY N, PEVERNAGIE D, "Standard procedures for adults in accredited sleep medicine centres in Europe", Journal of Sleep Research, vol 21, issue 4, 357-368, August 2012

Manuscript received: 26.06.2014