ORIGINAL ARTICLE

Modulation of the Muscle Activity During Sleep in Cervical Dystonia

Elena Antelmi, MD[1,2]; Raffaele Ferri, MD[3]; Federica Provini, MD, PhD[1,2]; Cesa M.L. Scaglione, MD[2]; Francesco Mignani, RPSGT[2]; Francesco Rundo, MEng[3]; Stefano Vandi, RPSGT[1,2]; Margherita Fabbri, MD[4]; Fabio Pizza, MD, PhD[1,2]; Giuseppe Plazzi, MD, PhD[1,2]; Paolo Martinelli, MD[1]; Rocco Liguori, MD[1,2]

[1]Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy; [2]IRCCS Institute of Neurological Sciences, Bologna, Italy; [3]Sleep Research Centre, Department of Neurology, I.C., Oasi Research Institute (IRCCS), Troina, Italy; [4]Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal

Introduction: Impaired sleep has been reported as an important nonmotor feature in dystonia, but so far, self-reported complaints have never been compared with nocturnal video-polysomnographic (PSG) recording, which is the gold standard to assess sleep-related disorders.
Methods: Twenty patients with idiopathic isolated cervical dystonia and 22 healthy controls (HC) underwent extensive clinical investigations, neurological examination, and questionnaire screening for excessive daytime sleepiness and sleep-related disorders. A full-night video PSG was performed in both patients and HC. An ad hoc montage, adding electromyographic leads over the muscle affected with dystonia, was used.
Results: When compared to controls, patients showed significantly increased pathological values on the scale assessing self-reported complaints of impaired nocturnal sleep. Higher scores of impaired nocturnal sleep did not correlate with any clinical descriptors but for a weak correlation with higher scores on the scale for depression. On video-PSG, patients had significantly affected sleep architecture (with decreased sleep efficiency and increased sleep latency). Activity over cervical muscles disappears during all the sleep stages, reaching significantly decreased values when compared to controls both in nonrapid eye movements and rapid eye movements sleep.
Conclusions: Patients with cervical dystonia reported poor sleep quality and showed impaired sleep architecture. These features however cannot be related to the persistence of muscle activity over the cervical muscles, which disappears in all the sleep stages, reaching significantly decreased values when compared to HC.
Keywords: dystonia, sleep, cervical dystonia, nonmotor symptoms.

Statement of Significance
Impaired noctural sleep has been reported as an important nonmotor feature in dystonia. Here, we compared self-reported complaints assessed by questionnaires with objective recordings of sleep architecture and muscle activity over the muscles affected with dystonia by means of PSG, in a controlled cohort of 20 patients with idiopathic isolated cervical dystonia. Results showed an objective impairment of sleep architecture, but muscle activity over the muscle affected with dystonia decreased during all sleep stages, until reaching values relatively lower than that of the healthy controls. This leads to hypothesize a possible homeostatic role of sleep for the recovery of muscles affected with dystonia. The study highlighted that sleep impairment in dystonia deserves a specific treatment.

INTRODUCTION

Dystonia includes a broad range of patterned movements due to involuntary muscle contractions. According to the latest consensus update "dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal… movements, postures. …. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation".[1] What emerges is how one of the most peculiar features of dystonia is its relationship with movement and posture. Dystonic posture typically increases while holding a position or while performing movements, to the extent that task-specific dystonia is characteristically triggered only by certain movements (ie, playing an instrument, writing, singing, and eating).[2] Yet, on the same direction is the phenomenon of the overflow, which consists in the speeding of dystonic activity in contiguous muscles while performing an action. On the other hand, dystonic activity typically ameliorates while lying down or while holding the neck over a headrest.[3,4] It is now clear that most of these peculiar features are related to abnormal sensorimotor integration and inhibition within the central nervous system (CNS), as the result of a network disorder.[5,6]

From another viewpoint, normal sleep is the "gold standard" of motor quiescence because of the inhibition of the spinal motoneuron pool by supraspinal structures with consequent muscle hypotonia, until reaching an almost complete muscle atonia during rapid eye movement (REM) sleep,[7,8] except for the phasic activity emerging during REM.

Given these premises, it is reasonable to infer that dystonia would disappear during all sleep stages but phasic REM. However, the literature is confusing on this point and, as reviewed recently,[9] most of the previous studies were affected by biases related to the selection of small and heterogeneous groups of patients, lack of a control group, inclusion of medicated patients, and paucity of studies including both self-reported complaints of sleep problems and polysomnographic (PSG) recordings. Overall, it seems that impaired sleep is an important nonmotor feature in dystonia, negatively affecting quality of life of dystonic patients.[10–13] The prevalence of sleep impairment in focal dystonia has been reported to range between 40% and 70% in different cohorts.[9]

With this new study, we aimed to systematically and quantitatively investigate the activity of dystonic muscles during sleep stages by means of video-PSG, which is the gold standard for the assessment of movement during sleep, along with questionnaires measuring self-complaints of sleep and sleepiness, in a controlled homogeneous cohort of patients with idiopathic isolated cervical dystonia (CD).

METHODS AND PARTICIPANTS

Twenty consecutive patients with a diagnosis of idiopathic isolated CD, according to current criteria,[1] were prospectively recruited among those attending the outpatient clinics at the IRCCS, Institute of Neurological Sciences of the University of Bologna. Only patients with a clear diagnosis of idiopathic

isolated CD, according to the clinical records and to the neurological examination, were included in the study and among those who were asked to take part in the study, none refused. Twenty-two healthy participants matched for age and gender distribution (and negative family history for neurological disorders, including dystonia) served as healthy controls (HC). HC were recruited among acquaintances of the researchers. Additional exclusion criteria for both patients and HC were: (1) no history of other neurological or psychiatric diseases and (2) no history of medications acting on the CNS.

Patients were assessed at least 3 months after their last botulinum toxin injection. They all performed extensive neurological examination including history taking, clinical examination, and brain magnetic resonance imaging. Demographic information, including age, gender, and concomitant comorbidities was obtained from both CD patients and HC. Disease severity was assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Clinical examination, including evaluation of the pattern of dystonia and administration of the TWSTRS were performed by a neurologist with expertise in movement disorder (EA). In order to identify the main pattern of CD and the key muscles, we observed the patients in several different positions (ie, at rest, while sitting, while keeping the arms outstretched, and while walking). Regarding sleep-problem assessment, both CD patients and HC underwent a sleep interview excluding other sleep-related disorders, that is, presence of obstructive apnea or habitual snoring, presence of restless legs syndrome (RLS), according to current criteria,[14] self-reported quality of sleep was evaluated by means of the Pittsburg Sleep Quality Index (PSQI)[15] and presence of excessive daytime sleepiness (EDS) by using the Epworth Sleepiness Scale (ESS).[16] Mood was investigated by the Beck Depression Inventory (BDI).[17]

Both CD patients and HC underwent a full-night PSG. The PSG montage included conventional EEG, bilateral electrooculogram, submentalis and anterior tibialis electromyography (EMG), respiratory parameters, electrocardiogram, and infrared video.[18] Additional EMG leads were placed over the neck muscles affected with dystonia, that is, sternocleidomaistoideus (SCM) and splenius bilaterally and over the deltoid, contralaterally to the most affected side, and this latter served as a control muscle. Sleep signals were sampled at 200 Hz and stored on hard disk in European data format for further analysis. We decided to record the SCM and splenius muscles because they are the most frequently affected muscles in CD (even if not solely) and the easier to register by means of surface EMG leads. We decided to keep the montage as simple as possible to avoid provoking additional discomfort.

All patients were additionally asked to evaluate the level of discomfort/pain caused by their dystonia by means of a visual analogue scale (VAS, values 0 to 10) four times: (1) at the beginning of the recording (after all technical procedures), (2) after 20 minutes of relaxed wakefulness with eyes closed (with subcontinuous alpha rhythm on the EEG) before sleep, (3) on awakening, the following morning, and (4) after 20 minutes of relaxed wakefulness with eyes closed (with subcontinuous alpha rhythm on the EEG) after awakening.

All experimental procedures were approved by the institutional ethic committee and conducted in accordance with the Declaration of Helsinki and according to international safety guidelines. Both CD patients and HC gave their signed informed consent.

Sleep Staging and Muscle Activity Analysis

Sleep stages were scored according to the current criteria.[18] The following conventional sleep data were analyzed in nocturnal recordings: sleep latency (SL; defined as the first epoch of any sleep stage from lights off), and stage REM latency (REML) from sleep onset, total sleep time (TST), sleep period (SP; time from sleep onset to lights on), wakefulness after sleep onset (WASO), sleep efficiency (SE), absolute time spans and percentages (of TST) spent in nonrapid eye movement (NREM) sleep stages N1, N2, and N3, and in stage REM.

The activity of muscles affected with dystonia and control muscles was evaluated during the whole recording by using ad hoc software[19] and by measuring the average amplitude of the rectified EMG signal during 1-second long mini epochs and excluding all periods with large body movements or other types of technical artifacts.

Periodic leg movements during sleep (PLMS) were visually detected and marked, and the PLMS index was calculated according to standard criteria.[18]

Statistical Analysis

The comparison between the CD patients and HC data was carried out by means of the nonparametric Mann-Whitney test for independent data sets, the Friedman analysis of variance (ANOVA) for multiple dependent data sets, or the chi-square test for frequencies, as appropriate; a series of correlations were also investigated by means of the multiple regression analysis and the calculation of the partial correlation coefficients. p Value $\leq .05$ was considered significant. The commercially available software STATISTICA v. 8.0, StatSoft Inc. (2007) was used for all statistical tests.

RESULTS

Demographic features, neurophysiological data, and questionnaire results of CD patients and HC are reported in Table 1. Patients had a mean disease duration (years ± standard deviation) of 7.6 ± 5.7; mean value of the TWSTRS was 17.9 ± 5.9. Patients were mainly affected with torticollis or laterocollis, and in 12 patients, dystonia was associated with tremor involving the neck (Supplementary Table). Patients and HC did not differ for age and gender distribution.

The results of questionnaires assessing EDS and mood complaints were comparable between the two groups, but CD patients had significantly increased pathological values on the PSQI, assessing self-reported complaints of impaired nocturnal sleep. A multiple regression analysis was carried out with PSQI measuring self-reported sleep quality as the dependent variable and age, disease duration, TWSTRS, ESS, and BDI as independent factors, in CD patients; only BDI was found to be significantly correlated with PSQI (partial correlation 0.682, $p < .0032$).

When analyzing sleep architecture, we found that CD patients and HC differed for SE, which was significantly reduced in the CD patients group ($p < .005$); and SL and REML, which were significantly increased in the patients group ($p < .0038$ and

Table 1—Demographic Features, Neurophysiological Parameters, and Questionnaire Results Obtained From Patients and Controls.

Results	Patients (n = 20)	Controls (n = 22)	$p \leq .005$
Demographic data			
Age, years ± SD	50.5 ± 9.09	48.2 ± 6.19	ns
Females/males, number	14/6	11/11	ns
Questionnaries (mean scores ± SD)			
ESS	3.8 ± 2.5	2.4 ± 2.8	ns
PSQI	6.8 ± 5.6	2.3 ± 2.1	**.0009**
BDI	10.5 ± 6.1	9.1 ± 2.6	ns
Sleep architecture			
Total sleep time, minutes ± SD	368.6 ± 73.66	364.9 ± 67.8	ns
Sleep efficiency, % ± SD	75.7 ± 11.1	85 ± 8.9	**.005**
Sleep latency, minutes ± SD	36.9 ± 30.1	20.6 ± 17.1	**.038**
Sleep stage REM latency, minutes ± SD	118.5 ± 64.9	82.7 ± 44.7	**.042**
Sleep stage N1, % ± SD	10 ± 5.5	8.6 ± 6.3	ns
Sleep stage N2, % ± SD	48.2 ± 12.5	46.7 ± 8.5	ns
Sleep stage N3, % ± SD	20.6 ± 8.8	22.4 ± 9.2	ns
Sleep stage REM, % ± SD	20.4 ± 5	18.2 ± 3.9	ns
PLMS index, number/hour ± SD	4.3 ± 6.2	5.5 ± 10.5	ns
Arousal index, number/hour	16.8 ± 15.9	11.7 ± 7.4	ns

BDI, Beck depression inventory; ESS, Epworth sleepiness scale; ns, not significant; PLMS, periodic limb movements during sleep; PSQI, Pittsburg sleep quality index; REM, rapid eye movement; SD, standard deviation. Significant values are reported in bold.

$p < .042$, respectively). The multiple regression analysis considering the objective sleep parameters found to be abnormal in the above comparison, that is, SE, SL, and REML as dependent factors and all the clinical descriptors (age, disease duration, TWSTRS, ESS, PSQI, and BDI) as independent factors, in CD patients, disclosed only a significant negative correlation between SE and PSQI (partial correlation −0.533, $p < .04$) and a significant positive correlation between SL and PSQI (partial correlation 0.524, $p < .048$).

Analysis of Muscle Activity

Muscle activity during relaxed wakefulness (patients lying supine in bed) pre (Wpre) and post-night sleep (Wpost) over the muscles affected with dystonia (both the most affected one and the contralateral one) was slightly, but not significantly, higher than that of HC (Figure 1). In Wpre, activity over the control muscle (ie, deltoid contralateral to the most affected side) was significantly increased in CD patients, when compared to HC. In the different sleep stages (ie, stage N1–N2, N3, and REM), activity of dystonic muscles and control muscle progressively decreased from Wpre to N1, reaching significantly decreased values compared to HC in N3 and REM sleep stages in the most affected side, in N2, N3, and stage REM in the less affected side and in N3 in the control muscle (Figure 1).

When the muscle activity amplitude values were normalized by subtracting the individual mean amplitude during sleep stage REM (which is considered to be the gold standard for muscle atonia/hypotonia),[18] even if patients had a significant relative higher muscle activity over the neck muscles in Wpre, Wpost, WASO, and N1, they finally reached the same levels of muscle activity of HC in N2, N3, and stage REM (Figure 2).

Differently from the objective measurement of the muscle activity that soon after sleep returned to the values recorded before sleep, patients reported the severity of neck discomfort/pain to be reduced after nocturnal sleep as evident from the Friedman ANOVA ($p < .00001$) carried out on the four VAS evaluations obtained before and after night sleep (Figure 3). There was no statistical correlation between the different VAS evaluations and the objective muscle activity measurements during relaxed wakefulness before and after sleep.

DISCUSSION

This is the first study systematically analyzing activity on dystonic muscles during the different sleep stages and comparing neurophysiological data with results of self-reported questionnaires assessing EDS and quality of sleep in a representative cohort of patients with idiopathic isolated CD, compared to age- and sex-matched HC.

As far as the questionnaire assessment is concerned, our results confirm that dystonic patients reported a significantly reduced quality of sleep assessed by means of the PSQI, when compared to HC.[20–23] The analysis of the correlation between the other clinical descriptors and self-reported complaints of nocturnal sleep disclosed only a weak correlation with higher

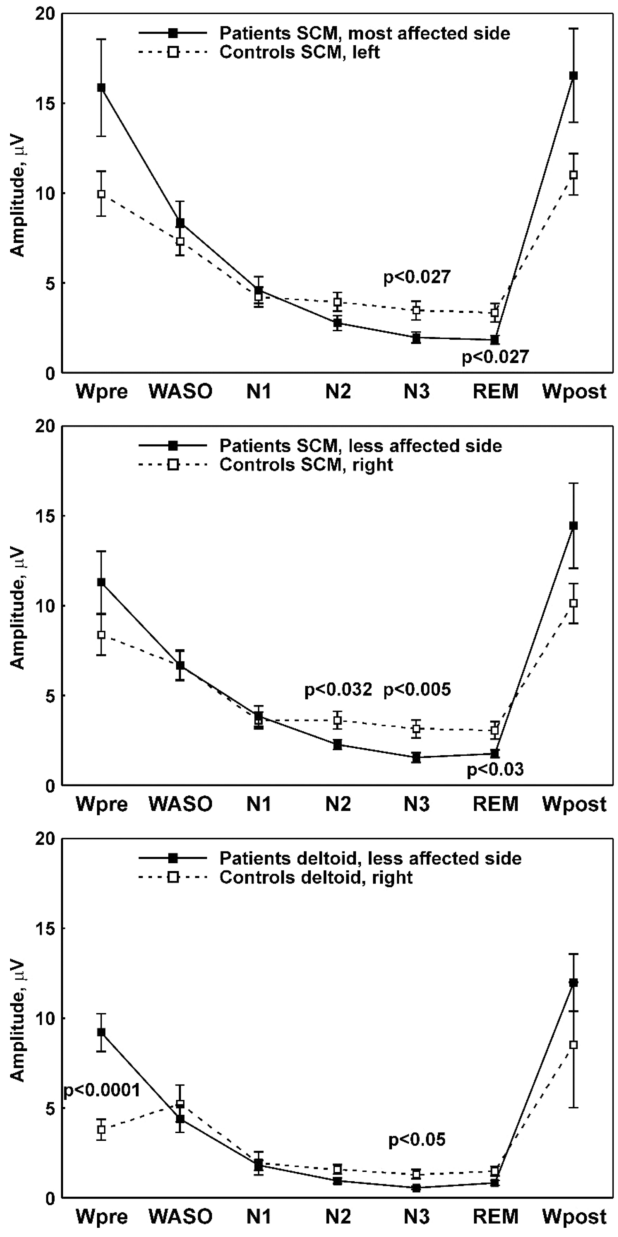

Figure 1—Comparison between the amplitude of the EMG signal in the different pairs of corresponding muscles recorded in patients and controls in the different wakefulness periods and sleep stages considered in this study. Values are shown as mean (squares) and standard error (whiskers). μV, microvolts; N1, N2, N3, stage 1, 2, and 3 of NREM sleep; REM, REM sleep; SCM, sternocleidomastoideus; WASO, wakefulness after sleep onset; Wpre, wakefulness pre night sleep; Wpost, wakefulness post night sleep.

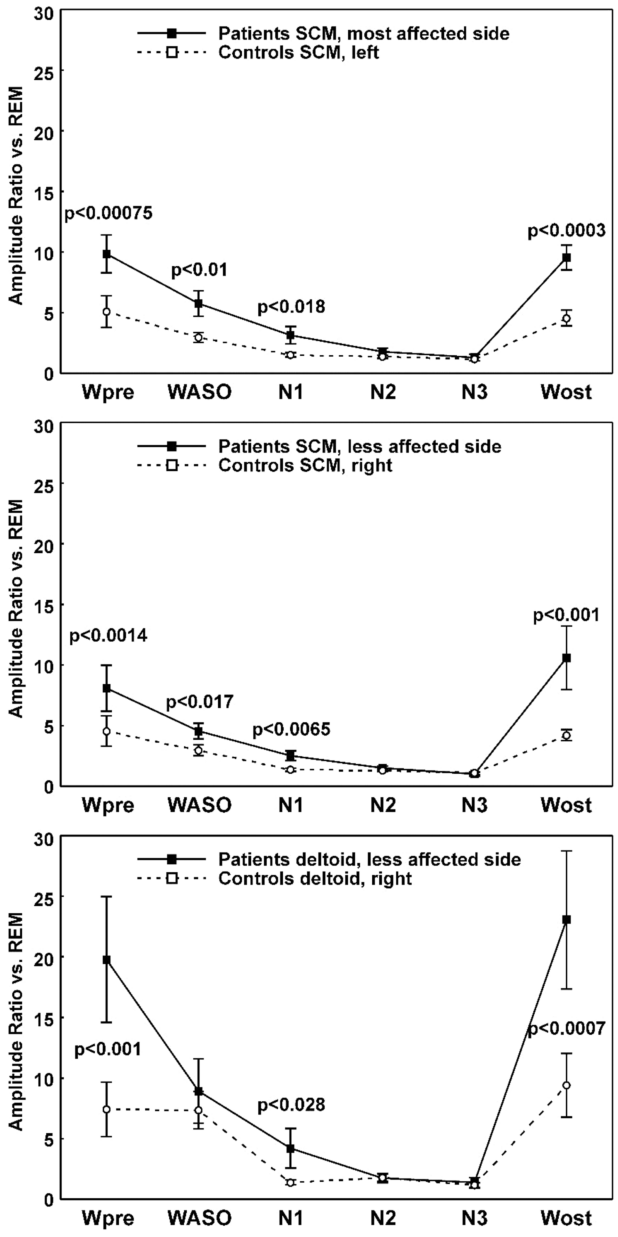

Figure 2—Comparison between the individually normalized amplitude (difference from that of sleep stage REM) of the EMG signal in the different pairs of corresponding muscles recorded in patients and controls in the different wakefulness periods and sleep stages considered in this study. Values are shown as mean (squares) and standard error (whiskers). μV, microvolts; N1, N2, N3, stage 1, 2, and 3 of NREM sleep; REM, REM sleep; SCM, sternocleidomastoideus; WASO, wakefulness after sleep onset; Wpre, wakefulness pre night sleep; Wpost, wakefulness post night sleep.

scores on the BDI, confirming the findings reported in previous cohorts,[21–23] and the known impact of mood deflection in quality of sleep.[24] Severity of dystonia and disease duration, instead, did not seem to affect the self-reported perception of sleep quality, in agreement with previous reports.[20,23] Interestingly, even if quality of sleep was self-reportedly reported to be affected, this does not seem to have an effect of the daytime complaint of EDS. ESS scores indeed were in the normal range and comparable to values in the HC. This finding conforms to what has been previously reported in patients with different types of focal dystonia,[21–23] except from one single study,[20] reporting higher percentage of dystonic patients with pathological ESS values, when compared to HC.

The analysis of sleep architecture disclosed a significantly decreased SE with difficulty in falling asleep (increased SL) and increased REML. Arousal index tended to be higher in CD patients as well, but this was not significant on statistical

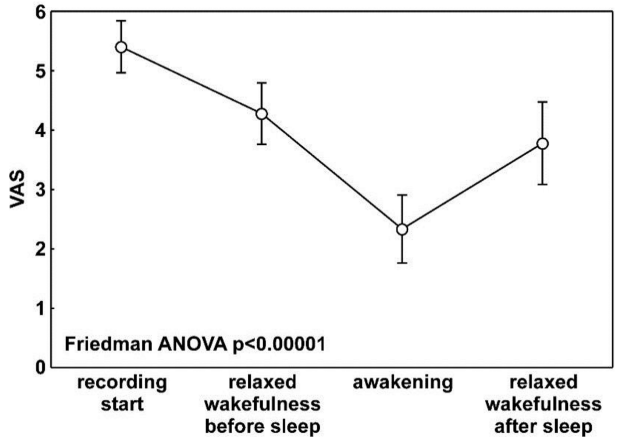

Figure 3—Self-reported level of discomfort/pain caused by dystonia in patients evaluated by means of a visual analogue scale at four different times, before and after sleep. Values are shown as mean (squares) and standard error (whiskers). ANOVA, analysis of variance; VAS, visual analogue scale for pain/discomfort.

investigation. Previous studies reported somewhat similar results. In 10 patients with cranial dystonia, Sforza et al. (1990) reported reduced SE, slow-wave sleep (SWS), and REM sleep and increased SL and arousals. Decreased SE and increased REML have been instead inconsistently reported in patients with CD.[3,25] In our cohort, the correlation between sleep architecture and clinical descriptors did not show an association with disease severity and disease duration. Of note, in the patients group, higher scores at the PSQI correlated with decreased SE and increased SL at the PSG recordings, indicating that self-reported complaints overlap with objective measurements of impaired sleep architecture.

Finally, a previous study in a cohort of patients with focal dystonia reported an increased incidence of RLS and bruxism in patients when compared to controls.[20] None of our patients had these complaints on clinical investigation, and PSG documentation failed to detect any significant additional sleep-related disorder; the presence of PLMs was comparable between CD patients and HC as well.

When analyzing muscle activity, it appears clear that activity over the muscles affected with dystonia, and even over the control muscle, progressively decreases to a great extent and almost disappears in SWS and REM sleep. Indeed, even if patients had (although not significantly) increased amplitude of muscle contraction during relaxed wakefulness, this amplitude reaches values which are significantly lower than those of HC, during both SWS and REM sleep. This finding was quite unexpected.

So far, very few PSG studies have been performed in patients with focal dystonia. Three of them reported persistence of muscle activity over the dystonic muscles both in patients with cranial dystonia[26,27] and with CD.[25] In the study by Sforza et al.,[26] the number of spasm per hour of sleep in the cranial region (patients with blepharospasm or Meige syndrome) progressively decreased during the night without disappearing and then gradually increased, particularly prior to awakening. Silvestri et al.[27] reported somewhat similar results, in a cohort of seven patients with cranial dystonia. However, these studies have been mainly conducted in small groups of patients, without a normal control group,[25–27] and results are reported in a descriptive fashion, without performing any statistics.[25] On the contrary, there is a single study (comparing nine patients with CD vs. nine HC)[3] reporting both supine position and sleep to be associated with an improvement of symptoms of CD, with abnormal cervical muscle activity decreasing immediately when lying down, without the intention to go to sleep and then being gradually abolished in all patients during the transition from relaxed wakefulness to light NREM sleep. Following this transition phase, no more abnormal EMG activity was found in any patient.[3]

Somehow surprisingly, our study goes further, showing not only the virtual disappearance of dystonic activity during SWS and REM sleep but also a significant decrease in muscle activity over the dystonic muscles and over the control muscle, when compared to muscle activity on homologous muscles in HC. Of course, the nature of our study does not allow us to reliably explain this aspect. However, we can speculate that also dystonic muscles activity might obey to the sleep-promoted homeostatic balance.[28] Accordingly, it might be inferred that a muscle, which has been (over)active all day long, might need a "deeper" rest at nighttime. Animal models show that at nighttime, hypotonia in cervical muscles is greater if compared with cranial muscles.[29,30]

However, studies reporting on modulation of EMG muscle activity at nighttime after exercise or training are lacking. Indirect observations might also suggest that increased activity during daytime induces homeostatic recovery during nighttime.[31,32] Physiologically, indeed, pioneering studies reported a major decrease in the EMG activity of antigravity skeletal muscle tone during sleep,[31] except for leg muscles,[33] thus suggesting a recovery function of sleep for those muscles more active during daytime.

In this regard, our findings raise important questions related to the pivotal role of sleep in regulating synapsis homeostasis and in influencing thalamocortical circuitry.[34] Indeed, it has been proposed that sleep weakens synapses through the process of "synaptic renormalization".[35] Even if the exact mechanisms underlying these processes are not fully understood, synaptic homeostasis would lead to adjustment of synaptic weights in a neuron or network. This form of downscaling, especially in dystonia, can somewhat temporarily offset the hebbian mechanism of long-term potentiation which, if left unrestrained, would instead saturate the neuronal network.[36] In this view, sleep in dystonia might try to reset synaptic weights and prevent "synaptic overload". Of course, the nature of our study prevents any conclusions on this topic, and future studies with a more extensive evaluation of muscle activity and of neurophysiological correlates are warranted in light also of the potential-related therapeutic advantages.

Alternatively, another explanation might be that, as elegantly shown in the study by Mayer et al.[37] and acutely observed earlier by Arnulf et al.,[38] at least during REM sleep, basal ganglia seem to be bypassed by the pyramidal system. Dystonia is known to be a network disorder,[5,6] and it is therefore possible that the sensorimotor cortex, released from the basal ganglia influence, might function in another way, "getting rid of dystonia". Indeed, during sleep, there is a breakdown of cortical effective connectivity,[39] and therefore, this could somehow reset abnormal connectivity and inhibition in dystonia.

Indirect observations suggest also an impairment of the GABAergic inhibitory system within the CNS in dystonia,[6,40] and physiological hypotonia during sleep is thought to be induced by glycinergic and GABAergic post-synaptic inhibition.[41]

In this view, the physiological displacement versus a GABAergic signaling during sleep could somewhat temporarily rescue the network. To further add to this reasoning, zolpidem, which is gamma-GABAergic agonist of the benzodiazepine subtype receptor BZ1, highly represented in the structures of the basal ganglia, has been often reported to ameliorate dystonic symptoms.[42]

In our cohort, the finding of a statistical significant sleep benefit on cervical pain/discomfort, evaluated by means of VAS soon after awakenings, added further evidence to this hypothesis.

Interestingly, in the relaxed wakefulness preceding sleep, while CD patients are lying down with head and neck in a rest position, activity on a proximal muscle contralateral to the most affected side was found to be higher than that of the homologous one in HC. This is also a novel observation and it can be speculated to be a form of overflow, related to the abnormal sensorimotor integration in dystonia.[5] This pattern cannot be seen anymore after nighttime sleep onset.

Overall, our results suggest self-reported complaints of poor sleep quality are coupled with an objective impairment of sleep architecture in patients with CD, with reduced efficiency of sleep and increased of latency prior to fall asleep. Impaired nocturnal sleep however cannot be correlated to the persistence of muscle activity, neither with disease severity. Therefore, it seems that other factors, over and above, must be related to the self-reported perception of poor sleep quality and to the abnormal sleep architecture. This notion has already emerged from the clinical observation because it has been reported that complaints of impaired nocturnal sleep did not improve following botulinum toxin injections, despite a robust improvement in CD severity[23] and did not correlate with the severity of dystonia.[21,22]

Yet, previous studies assessing quality of sleep in different types of focal dystonia, that is, both cervical and cranial dystonia[21–23,26]reported comparable results in self-reported complaints among these groups, pointing to an intrinsic mechanism of sleep disturbance rather than a direct effect of the dystonic muscle activity. This dichotomy suggests that sleep aberrations in idiopathic isolated dystonia require separate focus for an effective treatment and cannot be viewed as secondary complications of the motor elements of this condition. The GABAergic impairment related to dystonia[6,40] might be claimed to play a role in this regard, but the mechanisms driving to the abnormalities in sleep architecture remain so far obscure and further studies are warranted in this regard. Orexinergic and histaminergic pathways, which are both known to orchestrate sleep and wake occurrence and central motor control in a homeostatic regulation manner, for example, have been poorly investigated in patients with dystonia.

In order to further confirm the discrete nature of sleep abnormalities in dystonia, it would be important in the future to compare these data with those obtained from a cohort of patients with acquired forms of dystonia. Dystonia due to anatomical lesions of the basal ganglia indeed has been proven to be different from idiopathic dystonia, which is instead viewed as a network disorder.[2,6] Indeed, these two groups of patients respond differently to therapy and show differences in pathophysiological mechanisms.[43] Moreover, a more extensive montage and more discerning analyses are warranted in order to further confirm our findings. Indeed, we have to acknowledge that in our study only two cervical muscles were assessed. However, CD is usually a complex movement disorders where more than one pattern of aberrant postures might be detected and where several muscles are usually involved at the same time. Still, analyses looking at the microstructure of sleep or at the sleep dynamics might add new insights to this fascinating aspect of dystonia.

Intrinsic abnormalities of sleep, which is the time when homeostatic regulation occurs, might further hamper the lack of inhibition underlying dystonia, and to this regard, it remains also to be tested whether drugs known to improve self-reported sleep quality[44] or targeting SE (like histaminergic or orexinergic antagonists)[45] might be effective in improving not only sleep quality but also motor signs in dystonic patients.

Specific roles: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

E.A: 1A; 1B, 1C, 2A, 2C, 3A, 3B
R.F.: 1C, 2A, 2B, 3A, 3B
F.Provini: 1A, 1B, 3B
C.S.: 1B, 3B
F.M.: 1C
F.R: 1C
S.V.: 1C
M.F.: 1C
F.P.: 1B, 3B
G.P.: 1B, 3B
P.M.: 1A; 3B
R.L.: 1A, 2A, 3B

REFERENCES

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013; 28(7): 863–873.
2. Quartarone A, Siebner HR, Rothwell JC. Task-specific hand dystonia: can too much plasticity be bad for you? Trends Neurosci. 2006; 29(4): 192–199.
3. Lobbezoo F, Thu Thon M, Rémillard G, Montplaisir JY, Lavigne GJ. Relationship between sleep, neck muscle activity, and pain in cervical dystonia. Can J Neurol Sci. 1996; 23(4): 285–290.
4. Jahanshahi M. Factors that ameliorate or aggravate spasmodic torticollis. J Neurol Neurosurg Psychiatry. 2000; 68(2): 227–229.
5. Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord. 2013; 28(7): 958–967.
6. Antelmi E, Erro R, Rocchi L, et al. Neurophysiological correlates of abnormal somatosensory temporal discrimination in dystonia. Mov Disord 2017; 32(1): 141-148.
7. Dement W, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol. 1957; 9(4): 673–690.
8. Chase MH, Morales FR. Control of motoneurons during sleep. Chapter 12. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: WB Saunders; 2005.
9. Hertenstein E, Tang NK, Bernstein CJ, Nissen C, Underwood MR, Sandhu HK. Sleep in patients with primary dystonia: a systematic review on the state of research and perspectives. Sleep Med Rev. 2016; 26: 95–107.

10. Soeder A, Kluger BM, Okun MS, et al. Mood and energy determinants of quality of life in dystonia. J Neurol. 2009; 256(6): 996–1001.
11. Kuyper DJ, Parra V, Aerts S, Okun MS, Kluger BM. Nonmotor manifestations of dystonia: a systematic review. Mov Disord. 2011; 26(7): 1206–1217.
12. Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain. 2012; 135(Pt 6): 1668–1681.
13. Wagle Shukla A, Brown R, Heese K, et al. High rates of fatigue and sleep disturbances in dystonia. Int J Neurosci. 2016; 126(10): 928–935.
14. Allen RP, Picchietti DL, Garcia-Borreguero D, et al.; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. Sleep Med. 2014; 15(8): 860–873.
15. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2): 193–213.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14(6): 540–545.
17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4: 561–571.
18. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.1*. wwwaasmnet.org. Darien, IL: American of Academy Sleep Medicine, 2014
19. Ferri R, Manconi M, Plazzi G, et al. A quantitative statistical analysis of the submentalis muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. J Sleep Res. 2008; 17(1): 89–100.
20. Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. Parkinsonism Relat Disord. 2009; 15(10): 784–786.
21. Avanzino L, Martino D, Marchese R, et al. Quality of sleep in primary focal dystonia: a case-control study. Eur J Neurol. 2010; 17(4): 576–581.
22. Paus S, Gross J, Moll-Müller M, et al. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. J Neurol. 2011; 258(10): 1835–1840.
23. Eichenseer SR, Stebbins GT, Comella CL. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. Parkinsonism Relat Disord. 2014; 20(4): 405–408.
24. Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. Sleep Med Rev. 2013; 17(5): 377–390.
25. Rondot P, Jedynak C-P, Ferrey G. *Le torticolis Spasmodique*. Paris, France: Masson, 1981: 67–74.
26. Sforza E, Montagna P, Defazio G, Lugaresi E. Sleep and cranial dystonia. Electroencephalogr Clin Neurophysiol. 1991; 79(3): 166–169.
27. Silvestri R, De Domenico P, Di Rosa AE, Bramanti P, Serra S, Di Perri R. The effect of nocturnal physiological sleep on various movement disorders. Mov Disord. 1990; 5(1): 8–14.
28. Vyazovskiy VV. Sleep, recovery, and metaregulation: explaining the benefits of sleep. Nat Sci Sleep. 2015; 7: 171–184.
29. Lu JW, Mann GL, Ross RJ, Morrison AR, Kubin L. Differential effect of sleep-wake states on lingual and dorsal neck muscle activity in rats. Respir Physiol Neurobiol. 2005; 147(2-3): 191–203.
30. Kato T, Masuda Y, Kanayama H, Morimoto T. Muscle activities are differently modulated between masseter and neck muscle during sleep-wake cycles in guinea pigs. Neurosci Res. 2007; 58(3): 265–271.
31. Kleitman N. *Sleep and Wakefulness*. 2nd ed. Chicago, IL: University of Chicago Press; 1963.
32. De Mello MT, Silva AC, Esteves AM, Tufik S. Reduction of periodic leg movement in individuals with paraplegia following aerobic physical exercise. Spinal Cord. 2002; 40(12): 646–649.
33. Okura K, Kato T, Montplaisir JY, Sessle BJ, Lavigne GJ. Quantitative analysis of surface EMG activity of cranial and leg muscles across sleep stages in human. Clin Neurophysiol. 2006; 117(2): 269–278.
34. Frank MG. Sleep and synaptic plasticity in the developing and adult brain. Curr Top Behav Neurosci. 2015; 25: 123–149.
35. Tononi G, Cirelli C. Time to be SHY? Some comments on sleep and synaptic homeostasis. Neural Plast. 2012; 2012: 415250.
36. Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. Cell. 2008; 135(3): 422–435.
37. Mayer G, Bitterlich M, Kuwert T, Ritt P, Stefan H. Ictal SPECT in patients with rapid eye movement sleep behaviour disorder. Brain. 2015; 138(Pt 5): 1263–1270.
38. De Cock VC, Debs R, Oudiette D, et al. The improvement of movement and speech during rapid eye movement sleep behaviour disorder in multiple system atrophy. Brain. 2011; 134(Pt 3): 856–862.
39. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science. 2005; 309(5744): 2228–2232.
40. Garibotto V, Romito LM, Elia AE, et al. In vivo evidence for GABA(A) receptor changes in the sensorimotor system in primary dystonia. Mov Disord. 2011; 26(5): 852–857.
41. Chase MH. Motor control during sleep and wakefulness: clarifying controversies and resolving paradoxes. Sleep Med Rev. 2013; 17(4): 299–312.
42. Abe K. Zolpidem therapy for movement disorders. Recent Pat CNS Drug Discov. 2008; 3(1): 55–60.
43. Kojovic M, Pareés I, Kassavetis P, et al. Secondary and primary dystonia: pathophysiological differences. Brain. 2013; 136(Pt 7): 2038–2049.
44. Baandrup L, Glenthøj BY, Jennum PJ. Objective and subjective sleep quality: Melatonin versus placebo add-on treatment in patients with schizophrenia or bipolar disorder withdrawing from long-term benzodiazepine use. Psychiatry Res. 2016; 240: 163–169.
45. Herring WJ, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology. 2012; 79(23): 2265–2274.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2017
Submitted in final revised form March, 2017
Accepted for publication May, 2017
Address correspondence to: Elena Antelmi, MD, Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Via Altura 3, Bologna, Italy. Telephone: +05 14 966 964; Fax: +05 14 966 176; Email: elenaantelmi@gmail.com

DISCLOSURE STATEMENT

DISCLOSURES RELATED TO THE PAPER

None.

DISCLOSURES FOR THE PAST 12 MONTHS

G.P: Consultant for: UCB Pharma, Jazz Pharmaceuticals, Bioproject; F.Provini: Consultant for SANOFI; Lecture (fees from Bial); R.L: Advisory Board consultant for Biogen-Genzyme; Lecture (fees from Dynamicom Education and Scientific Press); E.A.; R.F; C.S; S.V; F.M; F.R; M.F; F.P; P.M have nothing to disclose for the past 12 months.