

Sleep Disturbances and Asthma Control: A Real Life Study

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SUMMARY The objective of the present study was to investigate the level of asthma control in real life and the relationship between Asthma Control Test (ACT) scores and sleep disturbances. Patients on control visits for bronchial asthma were asked to complete the ACT questionnaire and to answer 5 questions about their sleep quality (S5). It was found that asthma control was unsatisfactory in 44%. In all ACT classes the level of asthma control appeared to be inversely related to the presence of sleep disturbances: patients with good control reported less frequent and less severe sleep disturbances than uncontrolled subjects. However, a significant percentage of subjects (11-20%) with total control of asthma still had sleep disturbances that resulted in an impaired quality of life. Therefore in any asthma case with sleep disturbances a broader investigation is required whether that impairment is actually a result of asthma or some other co-morbidity. Thus it would be useful if patients who reported sleep disturbances despite good/total control of asthma and rhinitis were managed with a holistic clinical approach and underwent nocturnal polysomnographic monitoring.

According to international guidelines¹ the objective of asthma therapy is to reach and maintain an optimal level of disease control, namely by achieving clinical and functional objectives reflecting both doctors' and patients' viewpoints. Nocturnal cough, wheeze and breathlessness sometimes represent the first symptoms of asthma, and in some asthmatic people they are the best markers for a deterioration of asthma control. Nocturnal asthma is not a different condition from asthma; it is merely one feature of the disease, which tends to affect mainly those with severe airflow obstruction or instability. Overnight airways' narrowing occurs in normal subjects but, because of its small extent, does not give rise to any symptoms. Airways narrowing is much more apparent in asthmatic subjects;² a study highlighted that the mean overnight fall in the peak flow rate in normal people is 8%, whilst it is 50% in asthmatic patients.³ The extent of nocturnal airways narrowing in asthmatics

mainly depends on the sleep quality of the patient (an increase of the parasympathetic and a decrease of the nonadrenergic not cholinergic bronchodilating tone, hormonal changes) but also on airway cooling, supine posture and bed-related allergic factors (i.e. dust).⁴ Restoring sleep can be achieved with asthma control; however, disrupted sleep can also be due to the presence of co-morbidities (allergic rhinitis, sleep apnoea, gastroesophageal reflux) or sleep disorders unrelated to the respiration. As a result of this, it appeared relevant to assess sleep-related problems of asthmatics and to identify a possible correlation between the level of asthma control and the quality of sleep in order to understand whether unsatisfactory sleep could be ameliorated through better

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asthma control or whether other causes needed to be taken into consideration. Therefore, the purpose of this study was to investigate the level of asthma control in real life and to assess the relationship between Asthma Control Test (ACT)⁵ scores and sleep disturbances which were evaluated with a 5-item questionnaire.

MATERIAL AND METHODS

Bronchial asthma patients who presented as pneumological outpatients at the Department of Allergy & Respiratory Diseases of Genoa University for a scheduled visit from April to June 2007 were included in this study. While patients were waiting for their turn in the waiting room, the nursing staff asked them to complete the Asthma Control Test (ACT) questionnaire and to answer 5 questions about their sleep quality (S5).

The study was approved by the internal Ethics Committee and conducted according to Good Clinical Practice rules. All patients gave their written informed consent before enrolment.

ACT is an effective and validated instrument to evaluate the level of asthma control. The test was developed by Nathan and colleagues⁵ by means of a stepwise regression on data from a basic questionnaire made up of 22 items. Through a statistical analysis, 5 items were selected to investigate the presence, in the previous four weeks, of limitations at work or school due to asthma, the presence of diurnal and nocturnal symptoms, and the use of

rescue medications. Each question was assigned a score from 1 to 5; adding up the scores allowed to classify the disease as: totally controlled (total score of 25), well controlled (score between 20 and 24), or uncontrolled (score less than 20).

For a subjective assessment of sleep-related problems, the same patients were asked to answer 5 questions about sleep (S5), which were also assigned a score from 1 to 5. The aim of the S5 was to provide a simple score that comprised the whole range of symptoms related to disrupted sleep. The questions were selected through the following steps: first, a pool of 30 issues related to sleep limitations/problems was generated on the basis of the following sources: (a) a review of the recent literature on available sleep questionnaires, (b) discussions with expert neurologists and pulmonologists and (c) preliminary unstructured interviews with more than 100 adult outpatients who were referred to our outpatient department. The issues were randomly listed and administered to the patients, who had to indicate which of the 30 issues was experienced by them and the importance of each selected issue on a four-point scale (1 not important; 4 very important). Subsequently, we calculated: (a) the percentage of patients who indicated each issue as a consequence of their disease (frequency range: 0-100), (b) the importance (mean value) attributed by the patients to each issue indicated as a problem (range: 0-4) and (c) the overall score of the issue, defined as the product of the frequency and the mean importance divided by 100 (range: 0-4). This first phase generated a 5-item questionnaire where patients had

Table 1 Sleep-5 questionnaire (S5)

| | | | | |
|--|--------------|------------|----------|---------------|
| Question 1. Do you have difficulty falling asleep? | | | | |
| Not at all (1 point) | A little (2) | Fairly (3) | Much (4) | Very much (5) |
| Question 2. Do you wake up at night? | | | | |
| Not at all (1 point) | A little (2) | Fairly (3) | Much (4) | Very much (5) |
| Question 3. Are you tired during the day because you don't sleep well at night? | | | | |
| Not at all (1 point) | A little (2) | Fairly (3) | Much (4) | Very much (5) |
| Question 4. Do you have difficulty concentrating? | | | | |
| Not at all (1 point) | A little (2) | Fairly (3) | Much (4) | Very much (5) |
| Question 5. Do you feel nervous? | | | | |
| Not at all (1 point) | A little (2) | Fairly (3) | Much (4) | Very much (5) |

to indicate, on a Likert scale with multiple options (1 not at all, 5 very much) (Table 1), how much they were troubled by each problem.

Then the presence of rhinitis and rhinitis treatment (anti-histamines, anti-leukotrienes, local steroid therapy, drug combinations, or none) was assessed in the same population.

The analysis first correlated the ACT level with every answer on sleep quality; then the single answers were evaluated in relation to the patients' age, sex, presence or absence of rhinitis, and therapy.

A descriptive analysis of the relationship between sleep and ACT was done by Pearson's correlation coefficient. The statistically significant cut off value was set at $p < 0.05$. All statistical analyses were carried out using SPSS 13.0.

RESULTS

The data of 122 patients who had to undergo a control visit for bronchial asthma were gathered from April to June 2007. The patients' age ranged from 15 to 75, with an average age of 44.16 (S.D. 14.882). Forty-seven (38.52%) patients were male and 75 (61.48%) were female. FEV₁ values obtained by respiratory function tests ranged from 36% to 117% (mean FEV₁ 87.53 ± 15.329). In 29 out of 122 patients, no sensitization to common inhaled allergens was found; in 1 patient, the allergometrical tests were not available; whereas 92 patients showed sensitization to one or more inhaled allergens, of which 74 were sensitized to at least 1 perennial allergen. Ninety patients (73.8%) reported rhinitis symptoms of which 42 (46.67%) underwent rhinitis therapy in the form of anti-histamines, anti-leukotrienes and/or nasal steroids. Among the 42 patients undergoing rhinitis therapy, 9 took anti-histamines, anti-leukotrienes, and nasal steroids; 31 patients affected by asthma and rhinitis took anti-histamines and anti-leukotrienes; and 2 patients took only anti-histamines. Regarding asthma therapy, 13 patients took salbutamol as needed only, 63 patients underwent inhaled therapy with a steroid and LABA, and 42 patients also took anti-leukotrienes.

According to the results of the ACT questionnaires, the population could be divided into

3 groups: Ten (8.2%), 58 (47.5%) and 54 (44.3%) of the patients were categorized as group 1 (total control with ACT score of 25), group 2 (well controlled with ACT score between 20-24) and group 3 (uncontrolled with ACT score <20), respectively. A correlation emerged between sex and the level of asthma control according to the ACT: women had lower ACT scores than men ($p = 0.009$; mean 18.00 vs. 20.40).

Some correlations emerged between the level of asthma control and sleep. The analysis showed that, for each question, the score obtained from patients with total or good control of asthma was statistically significantly lower ($p < 0.001$) than that of patients with uncontrolled asthma. Therefore, in all three ACT classes, the level of control of asthma appeared to be inversely related to the presence and impact of sleep disturbances (the greater the control, the smaller the impact of sleep disturbances). However, it is important to note that 10 to 30% of the patients with total asthma control suffered from sleep disturbances that could impair, even significantly, their quality of life; they reported to be "fairly" troubled by the presence of the following sleep disturbances: difficulty in falling asleep (30%) and nocturnal awakenings (20%), which in turn caused tiredness during the day (10%), difficulty in concentrating (30%) and irritation (20%).

Another significant correlation could be demonstrated between sex and three sleep qualities; namely, women reported to be more troubled by the following qualities: difficulty in falling asleep ($p = 0.029$), nocturnal awakenings ($p = 0.008$) and daytime tiredness ($p = 0.035$). But there was no correlation between sex and the impact of missed sleep on subjective wellbeing, difficulty in concentrating or irritation. All questionnaires were analyzed and the percentage for every given answer was calculated. The results are reported in Table 2.

A comparison of the groups showed that patients with well controlled asthma reported less frequent and especially less severe sleep disturbances compared to subjects with an uncontrolled respiratory symptomatology. In particular, the group of patients with total control of asthma symptoms never answered "very much", and only one patient out of

Table 2 Percentage of patients who reported a sleep disturbance according to the ACT score

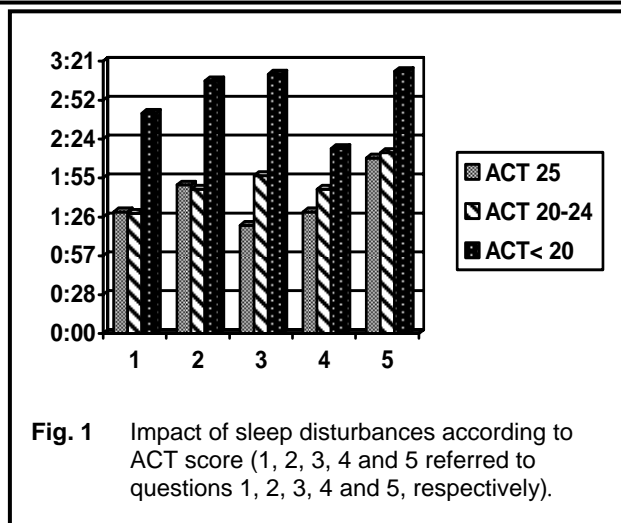
| Questionnaire | Not at all | | | A little | | | Fairly | | | Much | | | Very much | | |
|---|------------|-----------|---------|----------|-----------|---------|--------|-----------|---------|--------|-----------|---------|-----------|-----------|---------|
| | ACT 25 | ACT 20-24 | ACT <19 | ACT 25 | ACT 20-24 | ACT <19 | ACT 25 | ACT 20-24 | ACT <19 | ACT 25 | ACT 20-24 | ACT <19 | ACT 25 | ACT 20-24 | ACT <19 |
| I have difficulty falling asleep | 70% | 77.59% | 29.63% | - | 18.97% | 20.37% | 30% | 3.45% | 35.19% | - | - | 7.41% | - | - | 7.41% |
| I wake up at night | 70% | 65.52% | 18.52% | 10% | 25.86% | 24.07% | 20% | 6.90% | 38.89% | - | - | 11.11% | - | 1.72% | 7.41% |
| I feel tired during the day because I can't sleep well at night | 90% | 67.24% | 20.37% | - | 15.52% | 14.81% | 10% | 12.07% | 44.44% | 10% | 5.17% | 12.96% | - | - | 7.41% |
| I have difficulty concentrating | 70% | 62.07% | 30.19% | - | 31.03% | 37.74% | 30% | 6.90% | 20.75% | - | - | 7.55% | - | - | 3.77% |
| I feel nervous | 40% | 44.83% | 14.81% | 40% | 36.21% | 24.07% | 20% | 17.24% | 40.74% | - | 1.72% | 12.96% | - | - | 7.41% |

10 reported to be “much” disturbed by: “I feel tired during the day because I can't sleep well at night”. In all other cases, total control of asthma appeared to be associated with optimal or only slightly disturbed sleep. In patients with good but not total control of asthma, sleep disturbances were present in 22.41 to 55.17% and these disturbances were usually slight. Patients with ACT scores lower than 20 showed a more uniform distribution of answers, with a higher mean than the groups with total or good control. More precisely, 11 to 20% of the patients with uncontrolled asthma reported relevant disturbances with respect to both quality and quantity of sleep (Fig. 1).

The presence of rhinitis was assessed in all 122 patients with the aim to determine other causes that can lead to sleep disturbances; 90 were positive for allergic rhinitis out of which 42 received treatment for rhinitis. By using the *t*-test for data analysis, no statistically significant difference was observed between patients with asthma alone and patients with asthma plus treated or untreated rhinitis (Fig. 2).

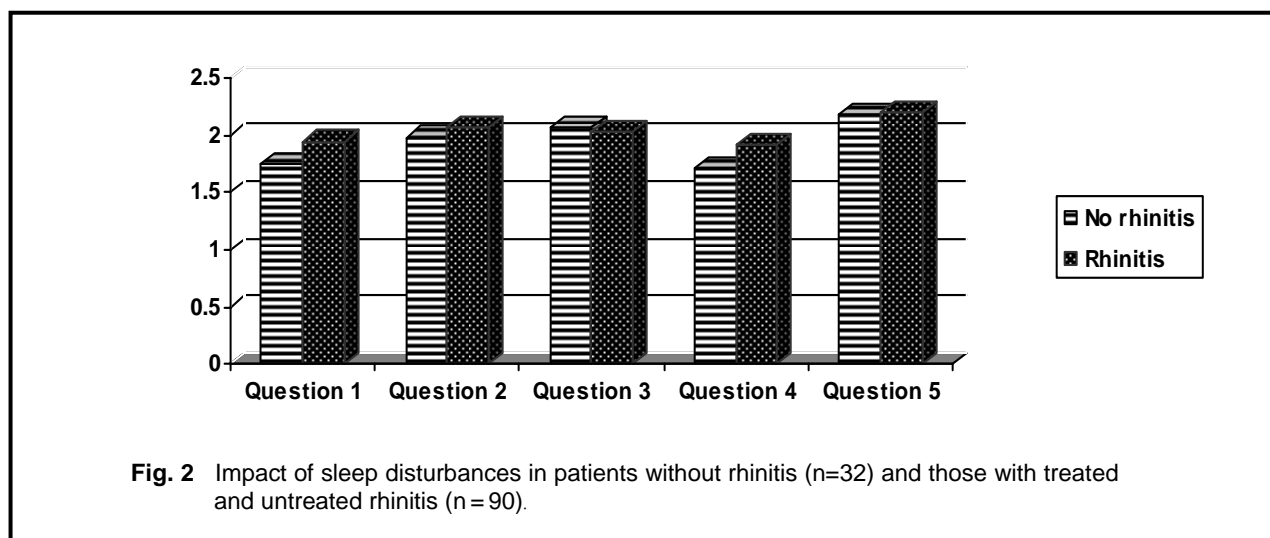
DISCUSSION

The objective of this study was the analysis of asthma control and sleep-related disturbances in a population of asthmatic patients who were referred to our specialist outpatient department for a control visit. Overall asthma control seemed to be unsatisfactory, as 44% of the sample did not achieve good control. This phenomenon involved especially women: in fact a correlation between difficulty in



falling asleep, nocturnal awakenings, daytime tiredness and ACT level of control could be noted in both sexes, but more prominently in females.

In all the three ACT classes, the level of asthma control appeared to be inversely related to the presence and impact of sleep disturbances, since patients with good control usually reported less frequent and especially less severe sleep disturbances in comparison to uncontrolled subjects. However, it is important to highlight that there was a significant percentage of subjects (11-20%) who still had sleep disturbances despite having achieved total control of asthma. The reported sleep problems, irrespective of the level of control achieved, contributed to an increase of the impact of the disease and to an impairment of life quality. Patients had difficulties falling asleep and maintaining sleep and additionally the rest was not restorative, which had an impact on mood and daytime functionality.



The prevalence of rhinitis in these asthmatic patients was 73%, confirming the percentage of rhinitis in the asthmatic population as reported by the literature.^{6,7} Since allergic rhinitis can cause sleep alteration, we conducted a sub-analysis of our sample in asthmatics and asthmatics affected by rhinitis (46.6% of which were under treatment for rhinitis). Despite the limits imposed by real life observation the results asserted that there was no significant difference between the relevance of sleep disturbances in patients with asthma alone and asthmatic rhinitis patients who did not need symptom therapy or did not have symptoms because of an asymptomatic status or because of anti-rhinitis treatment.

As it has been shown in different studies concerning sleep in adults with asthma, asthmatic patients have more difficulty falling asleep and maintaining sleep compared to healthy subjects.^{8,9} Significantly higher prevalence of difficulties inducing sleep (DIS), early morning awakenings (EMA), snoring, self-reported apnoeas, daytime tiredness (feeling physically tired during daytime), daytime sleepiness (feeling drowsy in the daytime), and a higher number of nocturnal awakenings were reported.

Asthmatic patients may also be at risk of sleep disorders because they are often administered high doses of nebulised or intravenous β -adrenoceptor agonists. Corticosteroid therapy can be a cause of sleep disturbances, especially if a high-dose is used,¹⁰ because it decreases slow wave sleep and

rapid eye movement sleep.¹¹ Aminophylline increases sleep latency, fragmentation and stage 1 sleep, while decreasing sleep efficiency and total sleep time along with the rapid eye movement and slow wave sleep phases.¹² This drug was also reported to cause nightmares. Janson *et al.*¹³ concluded that the sleep disrupting effects of theophylline were higher in caffeine sensitive individuals: theophylline and caffeine associated sleep disorders may be due to antagonism of central adenosine mediated central nervous system depression.

Obesity has been associated with an increased prevalence and incidence of asthma. However, the reason is unknown. Obesity reduces lung volumes, but it does not cause an alteration in the sensitivity or maximal response to methacholine. Nevertheless, obese subjects have an enhanced perception of dyspnea, with a greater apparent stiffness of the respiratory system, and therefore they are at greater risk of symptoms.¹⁴ Similar airflow limitation and bronchodilator responsiveness were reported by obese and non-obese subjects with asthma, but obese participants showed increased sleep disturbances and gastroesophageal reflux disease¹⁵.

Some previous studies showed that the prevalence of snoring and self-reported apnea was greater in asthmatic subjects.^{16,17} Sleep-related disorders other than snoring and apnea, such as difficulty in inducing and maintaining sleep and daytime sleepiness, were also associated with asthma.^{18,19} However, an epidemiologic study by

Klink and Quan²⁰ did not find any significant relationship with asthma as a solitary diagnosis because of the high prevalence of mild asthma that has a lot of symptom-free days. Further studies^{21,22} assumed an association between the obstructive sleep apnea syndrome and nocturnal asthma, by suggesting a relationship between asthma and sleep related disorders. There are different potential mechanisms by which asthma and snoring might be linked. For example, an increased drive to breathe asleep during active asthma could lead to increased upper airway suction pressures and thus to snoring. Alternatively, asthma may also be triggered by worsening of gastroesophageal reflux induced by snoring.²³ Nevertheless, the link between asthma and snoring might simply be that asthmatics are more likely to have upper airway inflammation (i.e. rhinitis) which predisposes them to snoring.

In conclusion, the “real life setting” provides an interesting static picture of health-related problems but it does not allow to draw conclusions about the observed phenomena. However, we can point out that a substantial proportion of patients with asthma currently experience suboptimal levels of asthma control, as has been mentioned in previous large population based studies.²⁴ We can also highlight that despite achieving a high or total level of control, a certain percentage of patients still experience sleep disturbances. Therefore, a broader investigation of the causes is required before imputing sleep impairment to asthma and increasing anti-asthmatic treatment.

The potential role of co-morbidities (such as rhinitis and gastro-oesophageal reflux), drug side effects, dyssomnias, parasomnias and medical/psychiatric sleep disorders must be considered. It would be useful if patients who report sleep disturbances despite good/total control of asthma and rhinitis were managed by a holistic clinical approach and underwent nocturnal polysomnographic monitoring.

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