

## Frequency of nocturnal symptoms in asthmatic children attending a hospital out-patient clinic

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**ABSTRACT:** Since nocturnal symptoms indicate more severe asthma, we investigated their frequency in a hospital-based population of asthmatic children. Recognition of these symptoms offers the possibility to introduce appropriate treatment.

We studied 796 consecutive children with asthma (mean (SD) age 9 (4) yrs) attending a hospital clinic, to determine whether these nocturnal symptoms predicted that daytime activities would be affected, and also the patients' perception of disease severity. At the end of a regular out-patient clinic visit, the answers to seven different questions concerning nocturnal symptoms in the previous 3 weeks were recorded. The forced expiratory volume in one second (FEV<sub>1</sub>) was  $\geq 90\%$  predicted in 98% of the population that was able to perform lung function measurements (72% of the total population).

In 38% of the patients with nocturnal symptoms, these symptoms were reported spontaneously. When asked for, nocturnal symptoms were reported by 47% of the children; 6% every night and 34% at least once a week. Cough was the most frequently reported symptom (31%). Children with nocturnal symptoms had a lower FEV<sub>1</sub>, scored their perception of asthma as more severe, and had their daytime activities affected more than those without nocturnal symptoms.

Doctors should specifically ask about nocturnal symptoms, as not all patients with nocturnal symptoms report them spontaneously and they predict more severe disease.

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A circadian variation in peak flow rate exists both in healthy subjects and asthmatics, with best lung function values during the day and worst values during the night [1–3]. The difference is due to a change in airway size at night [4]. Nocturnal dyspnoea, cough, wheeze, as well as dyspnoea on waking in the morning are common symptoms in asthmatic patients [5]. Dyspnoea on waking in the morning is an indicator of the nocturnal fall in lung function at night. In children, it may cause patients and their parents to wake at night, and may lead to poorer educational and cognitive performance [6–7].

Nocturnal symptoms of asthma have been recognized for a long time [8]. Since they indicate severe asthma, these symptoms would be expected to be common in a hospital-based population of asthmatics. We investigated the frequency and types of nocturnal symptoms in children with stable asthma, who regularly visited our out-patient clinic, and also their effect on perception of asthma severity and daytime activity.

### Patients and methods

#### *Study design*

Children who were regular clinic attenders participated in our study between September 1990 and September 1991. All answered seven different questions concerning nocturnal symptoms in the previous 3 weeks. Questions were answered either by the child or by the parents of younger children at the end of the out-patient visit after the usual history, physical examination and lung function tests had been completed.

#### *Patients*

All children were previously diagnosed as having asthma based on a history of recurrent episodes of wheeze, dyspnoea and coughing in response to allergens or non-allergic stimuli. History was taken according to the Dutch version

of the standardized questionnaire of the British Medical Research Council (MRC European Coal and Steel Community (ECCS) questionnaire) [9].

Patients with viral infections or asthma exacerbations during the out-patient visit were excluded from the study.

### Questionnaire

The questionnaire concerning nocturnal symptoms in the previous 3 weeks was administered by one of 4 authors (GGM, JG, KK, WMCvA). Spontaneously reported nocturnal symptoms were noted. For this study, questions concerning nocturnal asthma were, deliberately, not asked by the physician before the questionnaire. All medication was recorded.

The following questions were asked:

1. Do you (does your child) wake up at night due to: a) dyspnoea; b) cough; c) wheeze; d) do you (does your child) suffer from dyspnoea on wakening in the morning? Possible answers were yes or no [Type of symptoms].

2. How often per week do you (does your child) suffer from symptoms mentioned under 1? [Frequency].

3. Do you consider the severity of your asthma (the asthma of your child) as mild, moderate, severe or very severe? [Severity].

4. If there are nocturnal symptoms, do they generally influence activities during the next day?

The terms between square brackets are used to indicate the different questions in tables 1 and 2.

The study protocol was approved by the University Hospital Ethics Committee.

### Lung function measurements

In children aged 6 yrs and older (n=576), 72% of the population under study, forced expiratory volume in one second (FEV<sub>1</sub>) was measured with a water-sealed spirometer (Lode, The Netherlands). The best of three FEV<sub>1</sub> efforts was used for statistical analysis. Normal values from ZAPLETAL *et al.* were used [10].

### Statistical analysis

Statistical analysis was performed using SPSS/PC, version 4.0 (SPSS Inc., Chicago, USA). Values for age and

Table 2. – Subjective perception of severity of asthma by type and frequency of nocturnal symptoms

	Mild (n=401)	Moderate (n=304)	Severe (n=79)	Very severe (n=6)
<b>Type of symptoms</b>				
Dyspnoea at night	58	93	44	4
Cough	84	111	40	4
Wheeze	31	74	33	4
Dyspnoea on waking in the morning	53	98	44	3
<b>Frequency</b>				
0 or <1·week <sup>-1</sup>	329	164	26	2
1·week <sup>-1</sup>	27	31	12	-
2·week <sup>-1</sup>	14	38	10	1
3·week <sup>-1</sup>	10	26	8	1
4–6·week <sup>-1</sup>	10	18	12	1
Every night	11	27	11	1

FEV<sub>1</sub> had a normal distribution (Kolmogorov-Smirnov test), and are presented as means and standard deviations. The group difference for FEV<sub>1</sub> has been analysed with a Student's t-test. Comparison between children with one or more affirmative answer(s) to the questions on nocturnal symptoms, and those children who answered these questions negatively, have been analysed by Chisquared test. For the relationship of FEV<sub>1</sub> with the subjectively estimated severity grades, analysis of variance (ANOVA) was used. The analysis of the dependent variables for the estimation of subjective perception of the severity of the disease have been assessed with logistic regression and are presented as odds ratio (OR) and 95% confidence interval (95% CI). A difference of 5% was considered as significant.

## Results

### Patients

Patients (n=796; 512 boys (64%) and 284 girls (36%); mean (SD) age 9 (4) yrs) were labelled nocturnal asthma positive (NA+) when one or more of the questions on nocturnal symptoms were answered affirmatively, and nocturnal asthma negative (NA-) when these questions were answered negatively.

Table 1. – Subjective perception of severity of asthma by patients or their parents

	Total (n=796)		n	NA+ (n=375)		n	NA- (n=421)	
	n	%		%	% of total		n	%
<b>"Severity"</b> *								
Mild	401	50	127	33.9	16	274	65.1	34
Moderate	304	38	176	46.9	22	128	30.4	16
Severe	79	10	62	16.5	8	17	4.0	2
Very severe	6	1	6	1.6	1	-	-	-
Unknown	6	1	4	1.1	1	2	0.5	0

Total: all subjects; NA+: subjects with nocturnal asthma symptoms; NA-: subjects without nocturnal asthma symptoms. \*: significant differences between NA+ and NA- group, p<0.01.

FEV<sub>1</sub>

Ninety eight percent of the 576 children who performed lung function measurements had an FEV<sub>1</sub>  $\geq$ 90%pred. Mean FEV<sub>1</sub> values were significantly lower ( $p < 0.01$ ) in the NA+ group than in the NA- group ( $97.5 \pm 6.5\%$  and  $98.8 \pm 2.9\%$ , respectively).

## Type of symptoms and frequency

Almost half of the children (375, 47%) had nocturnal symptoms. Cough was the most frequently reported symptom (31%), although it often occurred in combination with other symptoms. Dyspnoea at night (25%), dyspnoea on waking in the morning (25%) and wheeze (18%) were less frequently reported. Nocturnal symptoms were present on every night in 6% of the children, and 34% reported having nocturnal symptoms at least once a week (table 3). The NA+ group used significantly ( $p < 0.01$ ) more maintenance medication (inhaled corticosteroids, cromolyn sodium, and ketotifen) than the NA- group (table 4).

Table 3. – Frequency of nocturnal symptoms in 796 children with stable asthma who were regular clinic attenders

Nocturnal symptoms	n	%
None	421	53
<1-week <sup>-1</sup>	102	13
1-week <sup>-1</sup>	71	9
2-week <sup>-1</sup>	65	8
3-week <sup>-1</sup>	46	6
4-6-week <sup>-1</sup>	41	5
Every night	50	6

## Subjective perception of severity of asthma

Subjective perception of asthma was considered to be mild or moderate in 88% of the children, and severe or very severe in 11% (table 1). Subjective perception of severity by patients in the NA+ group was significantly different from the NA- group ( $p < 0.01$ ); more children in the NA+ group regarded their asthma as severe or very severe. Mean FEV<sub>1</sub> values did not vary between the four groups with different subjective perception of severity grades (mild,  $n=317$ ,  $98.5 \pm 2.9\%$ ; moderate,  $n=212$ ,  $97.9 \pm 6.9\%$ ; severe,  $n=44$ ,  $97.7 \pm 2.7\%$ ; very severe,  $n=3$ ,  $99.4 \pm 1.3\%$ ; ANOVA  $p=0.47$ ).

Daytime activities were influenced by nocturnal symptoms in 33% of the total population, this was 46% of the NA+ group and 20% of the NA- group ( $p < 0.01$ ). The 20% of the NA- group were those who reported that before the 3 weeks of the questionnaire daytime activities were influenced by nocturnal symptoms.

Nocturnal symptoms were spontaneously reported in 25% of the total population, this was 38% of the NA+ group and 12% of the NA- group ( $p < 0.01$ ). The 12% of the NA- group were those who spontaneously reported that their nocturnal symptoms that were apparent before the 3 weeks of the questionnaire had disappeared.

Table 2 shows the distribution of type and frequency of nocturnal symptoms by perceived severity of asthma in the population. The difference between mild *versus* moderate, severe and very severe was discriminated by nocturnal wheezing (OR 2.45; 95% CI 1.54–3.94), dyspnoea on waking in the morning (OR 1.90; 95% CI 1.26–2.86) and the frequency of nocturnal symptoms (OR 1.35; 95% CI 1.20–1.52). Moderate *versus* severe and very severe disease were discriminated by dyspnoea at night (OR 2.31; 95% CI 1.36–3.94) and dyspnoea on waking in the morning (OR 1.90; 95% CI 1.12–3.22).

Table 4. – Patient medication

	Total (n=796)		NA+ (n=375)		NA- (n=421)	
	n	%	n	%	n	%
<b>None</b>	88	11	17	5	71	17
<b>Maintenance medication*</b>						
None	123	16	39	10	84	21
Corticosteroids#	398	50	190	51	208	49
Cromolyn sodium#	190	24	100	27	90	21
Ketotifen	85	10	46	12	39	9
<b>Bronchodilators</b>						
<b>Salbutamol#</b>						
Regular	159	20	98	26	61	15
On demand	423	53	222	59	201	48
<b>Ipratropium bromide#</b>						
Regular	24	3	18	5	6	1
On demand	1	0	1	0	-	-
Theophylline	22	3	18	5	4	1

Total: all subjects; NA+: subjects with nocturnal asthma symptoms; NA-: subjects without nocturnal asthma symptoms.

#: inhaled; \*: NA+ group used more ( $p < 0.01$ ) maintenance medication than the NA- group.

## Discussion

Although nocturnal symptoms are considered to be a common phenomenon in asthmatic patients, nothing is known about their frequency in a hospital-based population. In a cross-sectional survey in our paediatric population, approximately half of the patients suffered from nocturnal symptoms of asthma during the 3 weeks before their regular out-patient clinic visit. Nevertheless, 89% of the patients regarded their asthma to be moderate or mild. Patients with nocturnal symptoms of asthma had a significantly lower FEV<sub>1</sub>, reported often that their nocturnal symptoms influenced daytime activities, and assessed their asthma as severe significantly more often than those without nocturnal symptoms. Only 38% of the parents and patients with nocturnal symptoms reported it spontaneously. Results of the routine out-patient FEV<sub>1</sub> values were a poor predictor of nocturnal symptoms. Cough was the most frequently reported symptom.

CONNOLLY [11] estimated that one third of adult patients with asthma attending a clinic suffered from nocturnal symptoms. In 1988, TURNER-WARWICK [5] showed that 39% of the patients in a nonhospital-based population woke every night, 64% woke at least 3 nights per week, and 74% woke at least 1 night per week. These percentages were very close to those of a similar study by the same author 15 years earlier. It was, therefore, concluded that the frequency of nocturnal symptoms of asthma had not diminished despite the introduction of newer drugs, such as inhaled corticosteroids.

Our study shows a lower frequency of nocturnal symptoms than reported in the United Kingdom [5], a difference which is likely to be due to selection of patients. We studied a hospital-based population of asthmatic children, and the use of medication was not an inclusion criteria. TURNER-WARWICK [5] studied patients of no specified age to whom a general physician had prescribed or represcribed an aerosol bronchodilator. Differences in asthma management may be another factor. Our asthmatic children visit our out-patient clinic at least once every 6 months, where the clinical history is recorded, and a physical examination and spirometry are performed.

Medication use was not different between our population and the population studied by TURNER-WARWICK [5]. Forty eight percent of the latter study population also used inhaled corticosteroids, while 50% of our children used this type of medication. Despite the differences in outcome of the two studies, we conclude that nocturnal symptoms of asthma are still common, even in an asthmatic population regularly attending an outpatient clinic.

FOO and SLY [12] investigated baseline pulmonary function with symptom scores and home monitoring of peak expiratory flow (PEF) variability in 100 clinically stable asthmatic children from their out-patient clinic. They found that one third had an abnormal FEV<sub>1</sub>. We found that the majority (98%) of our investigated population had FEV<sub>1</sub> values within the normal range (FEV<sub>1</sub> ≥90% pred).

Nevertheless, we observed a high frequency of nocturnal symptoms indicating that the disease is not stable.

Cough was the most frequently reported symptom. FALCONER *et al.* [13] investigated the correlation between subjective reports of nocturnal symptoms and objective measurements of peak expiratory flow recordings and voice activated tape recordings of coughing. They found a poor correlation between subjective and objective assessment of nocturnal symptoms. Their observations indicate that our results, based on a questionnaire, may underestimate the real frequency of nocturnal airway obstruction or cough. However, waking up will probably have a greater impact on daytime activities than the frequency of recorded coughing sounds.

Dyspnoea on waking in the morning is a result of the nocturnal fall in lung function. In an earlier study, we observed that the 08.00 a.m. PEF value correlates well with the 04.00 a.m. value in a group of asthmatic children with increased airway obstruction overnight [3].

In the current study we labelled 375 (47%) of the population as having nocturnal symptoms. If we had not asked about dyspnoea on waking in the morning, 314 (39%) would have been labelled as having nocturnal symptoms. We would then have missed about 8% who slept through their nocturnal airway obstruction.

A surprising observation in our study was that nocturnal symptoms were only spontaneously reported in 38% of those experiencing them. It may be assumed that children and/or parents are accustomed to nocturnal symptoms and consider them as a normal feature. As nocturnal asthma is a sign of instability of asthma and associated with a higher rate of exacerbations [4], our findings have important implications for clinical practice. As stressed earlier by HENRY *et al.* [14], physicians should specifically ask for nocturnal symptoms, since these are often not spontaneously reported. Since asthma has different presentations and symptoms may differ with age group, we emphasize that all four symptoms should be asked about. Although we did observe significantly lower FEV<sub>1</sub> values in the group with nocturnal symptoms than in the group without nocturnal symptoms, the observed difference is small and mean FEV<sub>1</sub> values of both groups were in the normal range.

Our study indicates that routine out-patient clinic spirometry is a poor predictor for nocturnal symptoms. A more objective assessment of nocturnal airway obstruction is the measurement of PEF values on waking in the morning [3, 14]. This may help both parents and physicians to assess the severity of nocturnal airway changes. Moreover, it provides an indication of the severity of the disease and offers the possibility to introduce appropriate treatment.

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