Night cough and general practice research

L.J. TOOP, MB, MRCP
J.G.R. HOWIE, MD, PhD, MRCP, FRCGP
F.M. PAXTON, BA

SUMMARY. Thirty-four children, aged between three and nine years, presenting with nocturnal cough, were studied on successive nights using an automatic voice activated tape recorder system. Children with a family history of atopy coughed significantly more than children without such a family history. A wide variation in cough frequency was found both between and within subjects. No effects of treatment on cough frequency were demonstrated. Some of the physiological and pathological mechanisms underlying night cough are discussed.

Introduction

PERSISTENT nocturnal cough in children may represent a variant form of asthma. However, cough which appears worse at night frequently accompanies respiratory infection in normal children. A general practitioner is therefore often likely to be presented with night cough and it can be difficult to decide which coughs will respond to specific therapy.

This review discusses some of the physiological and pathological mechanisms underlying night cough, and looks at problems and possibilities for future study. The results from a preliminary research project are included.

Night cough

Incidence

Cough is the symptom most commonly presented in general practice. As many as one in four children may present with the symptom each year.1 As most coughs are, or seem, worse at night it is this element of coughing that is often reported.

An accurate estimation of the true incidence of night cough in the community would require a prospective study. Reviewing medical records, however, allows an estimation to be made of the frequency with which the symptom has been considered sufficiently important to be recorded. In a recent study of the medical records of a group of 214 seven-year-old children, 29% of the records examined contained at least one reference to 'night cough', 'nocturnal cough' or 'cough worse at night'. Of the children who had a history of night cough, some 45% were already or subsequently diagnosed as having asthma.2 The peak incidence of 'night cough' was when the children were between the ages of two and six years.

Presentation

Most studies have classified patients who cough by age and by provisional diagnosis.3-7 It may also be useful to consider night cough in relation to the duration of the symptoms.

Acute night cough commonly occurs as part of a general respiratory infection, when it is usually accompanied by daytime cough, by running nose and sometimes by fever. All these symptoms usually settle spontaneously within a few days.

Alternatively, night cough may become chronic, persisting for several weeks or months, and not usually accompanied by daytime symptoms or by constitutional upset. Children with this type of cough often suffer from other allergic conditions and have asthma. In these children the presence of wheeze is not essential to make the diagnosis, and the term 'variant asthma' has been used.8,9

Many night coughs seen in general practice fall into an intermediate group, in which the cough lasts for a period of perhaps two or three weeks, is ultimately self-limiting, but is troublesome nevertheless to both child and parent. As a number of these children also have atopic family backgrounds, reactive airways disease/asthma may be contributing to their symptoms.7 However, the importance of such a contribution is uncertain.

A prospective study aimed at exploring this problem is presented and discussed later in this review.

Pathology

Why do some children cough so much? In the case of the 'catarrhal child'10 postnasal drip has long been the putative cause.4,5,11 The proposed mechanism involves postnasal secretions trickling into the pharynx and stimulating cough receptors.11 A reflex throat clearing4,12 or constant4,13 cough results. The distinction between true coughing and throat clearing is sometimes unclear,14 and while this mechanism undoubtedly does occur in some children other authors do not consider that this is a common cause of troublesome cough.7 Even if postnasal drip is present in a coughing child the two are not necessarily causally related, for postnasal drip may occur coincidentally in a child with asthma.12

Following a viral infection several pathological changes occur in the respiratory tract and these may persist for several days or weeks. Mucosal damage may result either from direct viral attack, or through the action of released active immunological mediators. Disruption of the integrity of the epithelial surface permits the penetration of irritants to hypersensitized receptors,15 resulting in reflex cough and/or bronchoconstriction.

In sensitized individuals allergen inhalation, particularly of house dust mite faecal pellets, can also lead to cough and wheeze which is worse at night and on awakening. This exposure to antigen triggers the release of both short- and long-acting mediators which result in a combination of bronchoconstriction, inflammatory oedema and excessive mucus production.15

Why are night cough and wheeze interchangeable in some children with asthma? Either bronchoconstriction itself, by mechanically stimulating cough receptors, or the presence of excessive mucus may cause cough.11 In children mucus production may be more clinically apparent than wheeze, indeed parents sometimes report that after a night of coughing their children vomit mucus in the morning. It is known that mucociliary transport is less efficient during sleep in normal subjects,16 and in asthmatics it may already be impaired.15,17 When this first line of defence is overwhelmed, reflex coughing occurs. Mucus produced in this way is generally swallowed during sleep.

Non-asthmatic patients may show an increased reactivity to inhaled histamine or methacholine for several days after a respiratory infection.18 In those with asthma, however, this 'bronchial hyperreactivity' occurs independently of infection. It may be genetically determined,19,20 and it can be triggered by

multiple stimuli such as infection, exercise, cold air, the inhalation of allergens or irritants and perhaps even sleep itself.

It has been suggested that nocturnal asthma (and presumably also nocturnal cough in variant asthma) is simply a manifestation of this underlying bronchial hyperreactivity, and that the problem actually represents an exaggeration of the normal circadian fluctuation in airways resistance found in normal individuals. Evidence to support this theory comes from the observation that the diurnal variation in peak flow seen in normal patients is greatly exaggerated in patients with asthma. These fluctuations in peak flow may themselves be secondary to other circadian rhythms. The lowest level of circulating adrenaline occurs at 04.00 hours, and in those with asthma this correlates with measured rises of plasma histamine, and with the time of maximum bronchoconstriction. Adrenaline may therefore have a protective effect on the asthmatic airway, possibly by adrenergic stimulation of mast cells. The normal diurnal variations in circulating cortisol levels, and the suggested increase in vagal tone at night may also contribute to the increased bronchial tone responsible for the symptoms of nocturnal asthma.

The effect of sleep on bronchomotor tone is unclear. Sleep studies of adults with asthma have demonstrated wide fluctuations in airways resistance with the stage of sleep. In one study deep sleep (stages III and IV) was associated with a marked increase in airways resistance; however this is the very time when wheezy episodes occur least often. Nocturnal cough in adults with chronic bronchitis does not seem to occur in stage III and IV sleep, and parents also describe a cough-free period of one or two hours immediately after their child falls asleep; a time corresponding to the first period of deep sleep. Electroencephalographic studies of children with nocturnal wheezing again demonstrate the cyclical effects of sleep stage, although, as with adults, the mechanisms are far from clear. Perhaps deep sleep suppresses the cough reflex, which re-emerges as the child enters a lighter sleep stage, by which time the accumulated secretions trigger a protracted episode of coughing.

Children with asthma appear to spend significantly less time in the deeper stages of sleep than do non-asthmatic controls. However, the importance of these abnormal sleep patterns on concentration and performance at school is uncertain.

**Management**

Given the protective functions of the cough reflex during an acute infection it is illogical to attempt to suppress it. Although postnasal drip ought to respond to the drying effects of antihistamines, experimentally they do not alter the volume of respiratory secretions. In practice the antitussive effect of these preparations is minimal and they are contraindicated in those who may have retained secretions. The non-pharmacological management of acute night cough in otherwise normal children involves maintaining an even temperature and humidity, and avoiding irritants such as smoke and dust.

Children with variant asthma should receive conventional asthma therapy. Despite the short half-life of beta-receptor agonists, and the narrow therapeutic range of theophylline both have been shown to reduce the symptoms of cough and wheeze in those with asthma. Sodium cromoglycate may have a direct action on cough receptors, and on smooth muscle hyperreactivity, in addition to its traditional mast cell stabilizing effect. Therefore it should also be effective in treating the nocturnal cough of asthma.

Measures to reduce house dust have been shown to improve the symptoms of children with a proven allergy. Studies of adults with nocturnal asthma have also shown improvement of symptoms following strict allergen avoidance, but routine measures may be ineffective. On balance, it seems prudent to recommend the removal of dust traps, such as soft toys and thick carpets, from the bedrooms of children with nocturnal symptoms, and to replace any bedding containing feathers.

The optimal management of the intermediate group of atopic children who present with prolonged night cough after an infection is uncertain. As symptoms vary both in frequency and in severity, at present decisions about treating these children must remain a matter of personal choice. Opinion seems to favour the initiation of bronchodilator therapy on suspicion of asthma, and the presence of other diagnostic clues in the medical records may be helpful.

**Research project**

Patients' perceptions of cough severity are inevitably subjective and doubly so if a parent is reporting the symptom on behalf of a child. Accurate recall of night cough is further hampered by both the child and the parent (hopefully) being asleep for most of the observation period. The variable tolerance of parents to illness in their children, and the effects of previous diagnoses may also modify impressions of cough severity.

An objective method of measuring cough frequency is required to assess the effects of drugs, and tape recorder systems have been developed for this purpose. These systems all rely on a method of compressing several hours of recording onto short tapes for analysis. Most use a delay circuit and an acoustic switch to operate a reel-to-reel tape recorder. The first of such systems was described in 1964 and was used to examine the efficacy of antitussive drugs in adults with chronic cough from various causes. A similar system, used in 1966, again tested antitussive preparations in a group of hospitalized children. The system has been modified for use in several centres but has only recently been modified for home use in the general practice setting. The modification used in our study provided high quality recordings suitable for both quantitative and qualitative analysis.

**Subjects and method**

Thirty-four children aged between three and nine years were recruited to the study, which ran for 18 months. All of the children were said to have been coughing for a minimum of three nights (mean 20 nights, standard deviation 22). Children were excluded if there were any abnormal clinical signs on examination of the chest. The children were all visited at home by a nurse (F.P.) who installed the system and checked it each day. Each child was recorded for six hours, between 23.00 hours and 05.00 hours, on three successive nights. The children all received placebo syrup before they went to bed on night one; on nights two and three they randomly received (double blind) placebo, salbutamol or triprolidine.

**Results**

The mean cough counts for the six-hour periods of recording in the three treatment groups are shown in Table 1. The children are divided by the presence or absence of a family history of atopic illness which is here defined as a close family member having a history of asthma, hay fever or eczema. This information was collected at the time the tape recorders were installed. There is no apparent treatment effect in any of the treatment groups.

The children with a family history of atopy coughed on more nights when they were given placebo syrup (22 out of 28) than did the children without such a history (11 out of 30). This difference is significant ($\chi^2 = 8.7, P<0.01$).

The children with a family history of atopy also had higher cough counts on the nights when they were given placebo syrup (mean 75, standard deviation 130) than did the children without cough means.

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such a history (mean 15, standard deviation 47). Again this difference is significant \((t = 2.3, 56\) degrees of freedom, \(P<0.05\)).

The variation between patients was large, as was the variation for each patient on successive nights. Table 2 shows this night to night variation for the group receiving placebo on all three nights.

On initial qualitative analysis of the cough recordings several different patterns of cough were apparent. Some children coughed sporadically, while others coughed in bouts at intervals throughout the recording period.

### Problems

In several studies patients' and parents' subjective impressions of cough severity and treatment benefits have correlated poorly with objective cough frequency recordings.46-50 In our series parents tended to under-report coughing in the early hours of the morning, at a time when they themselves were asleep; very little over-reporting was found.

The use of diary cards to assess the efficacy of asthma therapy and antitussive drugs has been popular in the past, but again their reliability in accurately assessing night cough has been questioned.49 Because of these problems drug licensing bodies insist on objective cough counting for studies on antitussive preparations.51 The base-line variation found in our study has also been found in most other similar studies, even of subjects with chronic cough.48,49 The size of this base-line variation has important implications for the planning of future clinical trials which rely on the analysis of crude cough counts. Given this

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of children in group</th>
<th>Cough counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo on all three nights</td>
<td>6</td>
<td>6 0–21</td>
</tr>
<tr>
<td>Salbutamol on nights 2 and 3</td>
<td>5</td>
<td>0 0</td>
</tr>
<tr>
<td>Triprolidine on nights 2 and 3</td>
<td>7</td>
<td>16 0–50</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 2. Within subject night to night variation in cough count for the group receiving placebo on all three nights.

<table>
<thead>
<tr>
<th>Cough counts</th>
<th>Night 1</th>
<th>Night 2</th>
<th>Night 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children without a history of atopy</td>
<td>0 0 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 0 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 0 254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 21 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21 6 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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base-line variation and an agreed statement of a minimum treatment effect considered worthwhile, it would be possible to calculate the size of trial necessary to have an acceptable chance of demonstrating such an effect if present — this is referred to as the 'power' of a study.12

Several practical considerations relevant to future tape recorder studies in general practice seem worthy of mention.

**Technical considerations.** In the home setting it is difficult to standardize the time interval between medication and the start of the recording session. In addition it is impossible, without the continuous presence of a trained investigator, to start recording at the time the child falls asleep. Another problem is that children under five years of age have a tendency to forsake their own bedrooms for the comforts of the parental bed, often half way through a recording session.

**Interpretation.** The definition of one cough requires prior agreement — all sounds, all sounds between successive inspirations or all sounds between pauses. The methods of statistical analysis to be used should also be agreed before the trial. Various parametric and non-parametric methods have been used and in one study statistical analysis was said to be unnecessary!

### Suggestions for future study

Hospital-based studies on the mechanisms of night cough in asthma and its relationships to sleep and also on optimum drug therapy are continuing.

If general practice disease indexes were to include a list of all atopic families, it should be feasible to define a group of high-risk children, and to match them with non-atopic controls. It would then be possible both to observe the onset of asthma in high-risk children and also to prospectively compare the duration and frequency of respiratory symptoms in the two groups.

How can we decide which coughs in which patients will respond to bronchodilator therapy and can we say whether the response will be measured in terms of shortening of the illness, or the quantity of symptoms within the illness, or both? Given that the symptoms of the intermediate group with prolonged night cough after a respiratory infection are ultimately self-limiting, a testable hypothesis might be: 'Do bronchodilators significantly shorten the duration of prolonged night cough in any definable group of children?' In this situation the endpoint of cessation of cough should be a readily definable outcome.

To test the hypothesis: 'Do bronchodilators provide symptomatic relief for night cough in these children?' presents greater problems. Diary cards are unreliable and therefore tape recorders will be required. Given the inherent variability of the symptom, studies will also need to be large.
Studies of flow dynamics have demonstrated that a series of coughs following a single inspiration are necessary to clear secretions from small airways, whereas single large volume coughs are necessary to clear larger airways and the pharynx. Further qualitative analysis of the 'shape', composition and patterns of recorded sounds may allow the recognition of a distinctive cough in asthma.

Conclusion

The results from this preliminary study support the subjective impression that children with a family history of atopy cough more than those from non-atopic backgrounds. The numbers studied were too small to allow comment on treatment effects.

The mechanisms underlying night cough are far from clear, and the interplay of several pathways results in a changing clinical picture which is difficult to objectively evaluate.

Many normal children with acute night cough require no treatment but children with variant asthma deserve recognition and logical therapy. Further studies of the children from the intermediate group are required to clarify their likely response to bronchodilator therapy.

References

37. Spelman R. Chronic or recurrent cough in childhood—a presentation of asthma? J R Coll Gen Pract 1984; 34: 221-222.

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Address for correspondence

Professor J.G.R. Howie, Department of General Practice, University of Edinburgh, Levenhouse, 20 West Richmond Street, Edinburgh EH8 9DX.