

REVIEW ARTICLE

An Unidentified Monster in the Bed – Assessing Nocturnal Asthma in Children

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ABSTRACT: Nocturnal asthma (NA) is increasing in prevalence, affecting millions of people worldwide. In addition to being associated with increased mortality, NA is associated with a decreased quality of life. NA associated sleep disturbances and increased daytime sleepiness are especially important in children due to the accompanying behavioral and developmental difficulties. As diurnal spirometry is not a practical tool for the diagnosis and monitoring of NA, self or parental reports are used. Children underreport and underestimate their NA symptoms and parents are not fully aware of their child's NA indicators. In addition, there is the lack of physician familiarity regarding the assessment and treatment of NA. Therefore, NA is chronically underreported. The development of a non-invasive, objective, home-based diagnostic tool is crucial in diagnosing and monitoring children with NA. The presence of wheeze during sleep has been successfully employed as a tool to measure NA in children. This review discusses the increasing prevalence of NA, current diagnostic tools and the consequences of undiagnosed NA in children. In conclusion, this paper suggests that an automated wheeze detective device is an objective and practical tool to aid the diagnosis and monitoring of NA.

KEYWORDS: Nocturnal asthma, Sleep disturbances, Children, Wheeze

INTRODUCTION

Approximately 300 million people worldwide suffer from asthma with the prevalence increasing by 50% each decade (1). In children, asthma is the most common chronic illness worldwide (2). Nocturnal asthma (NA) is defined as any nighttime worsening of reversible airway disease associated with an increase in symptoms and airway responsiveness (3). NA symptoms, such as awakenings, cough, wheeze and dyspnea were reported in 47–75% of asthma patients in a number of extensive surveys from different countries (4-6). Objectively, NA is defined as a diurnal reduction in forced expiratory volume in one second (FEV1) of greater than 15% (7). However, as will be discussed in this review, acquiring diurnal spirometric data for the diagnosis and management of NA is difficult, time-consuming and expensive. Therefore, NA is usually

identified and monitored by nocturnal symptoms, increased nighttime asthma medication and daytime sequela.

SOURCES OF NOCTURNAL ASTHMA

A specific cause of NA has not yet been clearly defined. NA has the characteristics of a circadian disorder, a sleep-related induction of asthma and a more severe form of asthma. While everyone experiences a circadian-based nadir in lung function in the early morning, patients with NA experience a greater than normal diurnal decrease in airway function independent of sleep. The three main features of asthma - airway obstruction, inflammation and bronchial hyper-responsiveness - are all linked to a circadian nadir at 4 am (8, 9). This suggests the influence of circadian rhythms causing the nocturnal impairment of lung function (10). In addition, sleep can exacerbate lung function aggravation (11, 12). Confounding factors associated with sleep, such as the supine position of sleep and sleep-related disorders - i.e. Gastroesophageal Reflux Disease (GERD) or Obstructive Sleep Apnea (OSA) - worsen the lung function of asthmatics during sleep and hinder the determination of

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the role of sleep in NA (13-17). Increased asthma severity does correlate with a greater risk of NA, but NA is not dependent on severe asthma (18-20). Interestingly, a specific polymorphism of the β_2 -adrenergic receptor has been linked with NA, but not with more severe asthma, indicating the role of genetics in NA (21, 22). The mechanism of this polymorphism's correlation to NA has not been elucidated (22, 23). Additionally, exogenous triggers such as allergens and non-allergic stimuli may provoke NA. The origin of NA is not yet known; however it is likely multi-factorial and based on the patient's unique genetic, physical and environmental characteristics.

LINK TO MORTALITY

NA is linked to an increased risk of mortality, with 70% of deaths and 80% of respiratory arrests caused by asthma occurring during nocturnal hours (24, 25). A large nocturnal variation in peak expiratory flow (PEF), as observed in NA, is not correlated with asthma severity. However, it is an independent risk factor for respiratory arrest (24). This demonstrates that NA, independent of asthma severity, is correlated with asthma-related mortality. In a 7-year follow up study of Italian young adults with asthma, NA symptoms such as nocturnal dyspnea and nocturnal tightness were correlated with a two-fold increase in subsequent overall mortality (26). Additionally, a Canadian case-control study demonstrated an increased risk of mortality for asthmatics with nocturnal symptoms (27). NA patients have been found to have 5-to-6 times more risk of accidental death than the general population, which may be attributed to nocturnal symptoms interfering with their daytime attentiveness (26). In addition, nocturnal oxygen disruptions resulting from NA lead to an increased production of potentially dangerous free radicals (28). Therefore NA must be treated as a serious chronic disorder as it is correlated to an increased rate of mortality.

INCREASING PREVALENCE OF ASTHMA

Asthma has been increasing worldwide and based on the increase of two correlating factors, obesity and old-age, it is likely to continue increasing (29-31). Obesity has been shown to be associated with an increased risk of asthma in both children and adults (32, 33). As the incidence of obesity in children and adults rises, asthma rates are expected to increase (34, 35). Additionally, NA has been reported to be more prevalent in the elderly (36). The percentage of the elderly population worldwide is expected to continue to rise in the coming years as the baby boomer generation ages and medical advances allow for longer lives (37). Moreover, an increase in childhood asthma symptoms has been

observed in recent years and is expected to continue (38, 39). In accordance, Garner and Kohen found an increasing incidence of childhood asthma in Canadian children aged 0-5 and 10-11 (40). Whether this increased prevalence is based on an improvement in a physician's ability to diagnose asthma or a rise in the causes of asthma is unknown. It is important to consider the vast majority of information on asthma prevalence in children comes from epidemiological studies involving school-based surveys. In developing countries this would institute a sampling bias as many children from lower-income families do not attend school or go home early to help provide for the family. Compounding this, socioeconomic status is negatively correlated with asthma severity and nocturnal symptoms (41). Thus, the rates of asthma may be higher than reported in developing countries. As the number of asthmatics rise, tools for effective diagnosis and monitoring of NA symptoms will become increasingly vital.

UNIQUE MECHANISM OF NOCTURNAL ASTHMA

Diurnal FEV1 is an objective test for NA, though it does not account for subjective symptoms. Morgan et al. reported that the FEV1 of NA patients was on average 31% lower in the early morning than in the previous afternoon, but no detectable changes in the respiratory rate or expiratory duration were found during sleep (42). This demonstrates that the NA patient may not take action during sleep to compensate for a lack of oxygen. This can lead the asthmatic to undergo intermittent or acute hypoxia which can increase the levels of reactive oxygen species (ROS) leading to pathological effects (28, 43). Additionally, nocturnal asthmatics do not undergo the normal asthmatic adaptive response of increasing lung volume to combat increased airway resistance and maintain airway patency (44). This relationship does occur in asthmatics without NA and in non-asthmatics, indicating a unique mechanism of bronchoconstriction in NA (44).

DIURNAL SPIROMETRY TO ASSESS NOCTURNAL ASTHMA

The gold standard for the identification of asthma is clinical history, physical examination and laboratory spirometry with challenge testing. Spirometry demands a skilled technician to guide technique and interpret results. It is impractical for a technician to collect the required nighttime and morning spirometric data to accurately assess NA. To overcome this problem, the European Respiratory Society recommended day-to-day home spirometry for child asthmatics to measure

variation in pulmonary function (45). Initially, mechanical meters were used and the patient was instructed to fill out a diurnal PEF diary. However, it was demonstrated that written PEF diaries were unreliable (46, 47). Electronic home spirometry devices that automatically record data were employed to combat this issue. However, the spirometric data had poor concordance with other parameters of asthma severity and thus was deemed not clinically useful (48). Additionally, home spirometry compliance and test performance varies greatly in children, providing a biased picture of changes in lung function (49). Home spirometry is also impractical for children, as it requires extensive training and follow-up to ensure proper testing technique (50). At present, there is no practical way to collect a child asthmatic's diurnal spirometric data.

SELF AND PARENTAL QUESTIONNAIRES TO ASSESS NOCTURNAL ASTHMA

The simplest and most common method of assessing NA is self-completed questionnaires. Self-identification of NA symptoms is very difficult since the patient must clearly understand the meaning of the questions posed towards them regarding wheezing, coughing and sleep disturbances and be conscious of their nighttime symptoms (51). Falconer et al. found that adults have poor agreement between subjective self-estimation and objective measurements of nocturnal cough, a common symptom of NA (52). Physicians are often unaware of their patients' NA symptoms as patients generally have an indifferent view of NA symptoms and do not regularly report them to their doctor (53). In their study of 13,493 asthmatics, Raheison et al. found that only 48% had agreement between their actual NA situation and what was recorded by their general practitioner (6). Moreover, 42% of patients who declared they had no nocturnal symptoms had NA according to objective tests (6). This demonstrates a striking inability of the patient and the doctor to declare and identify NA symptoms. Identification of NA is vital as patients with NA symptoms have the lowest awareness of inadequate asthma control (54). Children have more difficulty in self-diagnosing NA than adults, as they are generally less aware of indicators (55). Physicians must be aware of this and specifically question asthma patients, especially children, regarding their NA status.

For children, parental reports/questionnaires are often employed in addition to self-diagnosis (51). Cultural and educational conditions play an important role in the answering of these questionnaires (56, 57). Parents must understand the terms used to describe NA symptoms and literacy is required to complete

questionnaires. Parents often do not know when their child falls asleep, are unaware of most awakenings and are not able to identify nighttime wheeze (58). Less than 40% of parents with a child who is asthmatic report their child's NA symptoms appropriately (18). Moreover, NA is more prevalent and asthma more severe in areas of low socioeconomic status, possibly due to environmental factors (41). Parents in these areas are more likely to have lower literacy rates of the national language (59). Low parental literacy correlates directly with worse care measures for children with asthma possibly due to a lack of understanding of asthma symptoms and lack of ability to report symptoms to a physician (60). As such, the risk of underdiagnosis and undertreatment of asthma was higher in children from ethnic minority groups in the inner-city and from poorer neighborhoods (61). Parents of children at higher risk of developing NA due to environmental and socioeconomic factors do not accurately report their child's asthmatic status (62).

The accuracy of self-diagnostic questionnaires to identify and monitor a child's NA status has not been confirmed. Regarding daytime symptoms, self-questionnaires in children aged 7-12 are as accurate in diagnosing asthmatics as objective tests such as bronchial hyper-responsiveness testing (63). Additionally, recent research suggests child asthmatics as young as 7 dependably report their asthmatic status (64). However, no studies have specifically researched self-diagnostic questionnaires to identify and monitor NA. Nocturnal symptoms are associated with future asthmatic severity (65). Self-diagnostic questionnaires do not predict future asthmatic episodes in children under the age of 11, suggesting that these questionnaires may not be suitable to monitor NA (66). Sleep arousals are hard to self-diagnose as the child may have trouble remembering and reporting awakenings (67, 68). For example, Brooke et al. found poor agreement between recorded and recalled nighttime coughing in child asthmatics (69). In a study of students aged 10-12, 21% were not able to answer if they had nocturnal cough (70).

Generally, children report more asthma symptoms than their parents (70-73). Mallol et al. demonstrated that adolescents report higher symptoms of asthma, rhinitis, and eczema related symptoms than parentally-completed questionnaires (51). Sleep disturbance symptoms such as cough at night and awakening with wheezing during the past 12 months were reported significantly higher by the child than the parent (51). Nocturnal cough is reported significantly more by the child than by the parent (70). This is understandable since the child is more aware of their nighttime disturbances than the parent and may not necessarily

share this information with the parent. Parents of children over the age of 11 provide little to no more asthma information than is obtained through a child's self-assessment (74).

The lack of understanding of the term 'wheeze' in children impairs accurate diagnosis and asthma control. Riedler et al. reported difficulty for adolescents in understanding the term 'wheeze' (75). The difficulty in diagnosing wheeze is not limited to children. Levy et al. demonstrated that during daytime hours parents are unable to accurately assess the severity of their child's wheezing as compared to a physician or a computerized-acoustic analysis (58). In a study of India's physicians, a substantial percentage (33%) did not identify wheeze when shown in the International Study of Asthma and Allergies in Childhood ISAAC video sequences (76). Only 47% of physicians were able to identify nocturnal wheeze. Difficulty in recognizing nocturnal wheeze demonstrates the need for a more objective tool to diagnose NA associated wheeze.

Inability to identify and communicate a child's nocturnal symptoms may lead to NA being left undiagnosed, impairing treatment and leading to negative quality of life consequences for the child. For instance, a lack of awareness of NA symptoms in stable and treated child asthmatics led to poorer sleep quality and impaired daytime activity (77). Furthermore, children with nocturnal symptoms have an increased risk for future adverse asthma events (65). Constant monitoring of NA symptoms in children is crucial in order to prevent future asthma events and protect against daytime sequela.

NOCTURNAL ASTHMA ASSESSMENT

Nocturnal asthma is monitored by a combination of clinical history, subjective self or parental questionnaires and spirometry. The use of only spirometry or clinical history consistently underestimated asthma severity in a study of children (78). As diurnal spirometry is impractical and self or parental reports may be inaccurate, NA requires a home-based objective tool to increase monitoring efficacy. This is especially important in rural and low-socioeconomic areas where overnight clinical monitoring is problematic (79). Acoustic analysis of patients while they sleep allows for a non-invasive method for diagnosing and monitoring NA.

SNORING TO ASSESS NOCTURNAL ASTHMA

Snoring is correlated with NA symptoms in children (80, 81). Snoring may cause transfer of nasal mucus to the lower airway through upper airway vibration and increased suction pressures in the pharynx. This

allergen-laden mucus may induce an asthmatic episode. However, snoring is found in many more asthma patients than those with NA. Teodorescu et al. found that while 55% of adult asthmatics reported daytime sleepiness, 84% reported snoring with 38% reporting habitual snoring (82). Lu et al. reported a highly significant correlation between snoring and asthma in preschool children indicating snoring could be used as a diagnostic symptom of NA (81). However, an asthma prevalence of 28% was reported while snoring was found in 10.5% of children. This indicates that snoring may too unspecific for NA diagnosis. Studies have not confirmed a snoring parameter (length, volume) that correlates to other NA symptoms or daytime consequences (83). The results indicate snoring alone is not appropriate for the assessment of NA.

NOCTURNAL WHEEZE

Wheezing is defined as a high to low-pitched continuous musical sound judged to be of significant duration (84). Wheezing with unforced breathing is associated with the severity of airflow obstruction and thus is a good determinant for assessing asthma control (85). In addition to asthma, wheezing in children may be triggered by acute determinants such as bronchitis, bacterial tracheitis, laryngotracheobronchitis or chronic causes such as GERD, cystic fibrosis, or bronchopulmonary dysplasia (86). Children with frequent wheezing symptoms but no asthma diagnosis experience illness-related morbidity similar to diagnosed asthmatics (87). Thus nocturnal wheezing, in the absence of asthma, requires adequate identification of the underlying health issue. A lag-time of approximately two years has been reported between the first recognition of wheeze and consulting a physician for treatment (88). This indicates a lack of public awareness of nocturnal wheezing and its effects on asthmatic control and overall quality of life. Education of general practitioners and patients is required so that wheezing is not overlooked and is treated as a symptom of a possible underlying health issue.

NOCTURNAL WHEEZE TO ASSESS NOCTURNAL ASTHMA

Measurement of nocturnal wheeze has been employed as a non-invasive technique to assess NA (89, 90). Kiyokawa et al. recorded intermittent tracheal sounds in asthmatic patients and controls during sleep (91). A respiratory physician performed an auditory review and manually recorded the presence of wheezes. Although time consuming for the analyst, this method provided objective home-based information that positively correlated with subjective symptoms and inversely correlated with morning PEF. Many characteristics of

wheezes, such as amplitude, frequency range, number of simultaneous wheezes, duration and chest distribution can be recorded and measured. The parameter that best correlates with other clinical indices of asthma is total wheeze duration as a percentage of sleep (92). The use of computerized automatic acoustic monitoring devices allows for objective wheeze detection without a physician reviewing nocturnal recordings. Computerized monitoring of the percent of sleep spent in wheeze, irrespective of the respiratory phase or site, was employed as the quantitative measurement in children and produced objective results with good sensitivity (93). The same wheeze monitoring method established that the presence of wheeze correlates to less than 51% of the expected morning FEV1 and a large diurnal variation in FEV1 (94). Although not used for the diagnosis of NA, lung sound analysis with computerized analysis of wheezing and crackles was suitable for the diagnosis of bronchiolitis in infants (95). The use of computerized acoustic analysis of nocturnal wheeze is an objective, home-based method that can be used in the determination of NA and other pulmonary disorders.

SLEEP QUALITY OF NOCTURNAL ASTHMA PATIENTS

In stable diagnosed child asthmatics, knowledge of NA symptoms is required in order to properly medicate the patient and to accurately assess daytime psychological impairments which may result from poor sleep quality. Nocturnal symptoms such as wheezing, cough, sleep disturbances and daytime sleepiness are reported significantly more in stable asthmatic children with non-diagnosed NA than in non-asthmatic controls (77). Accordingly, children with well-controlled, stable asthma have poorer quality of sleep and lower morning PEF values correlating to inferior objective and subjective sleep measurement as compared to non-asthmatic matched controls (96). In children with NA there is no difference in REM latency, REM sleep, sleep latency, total sleep time, and percentage in sleep stages as compared to controls (1). This indicates that the problems are not due to sleep stage quantity but rather to sleep quality since children with NA have more sleep awakenings than non-asthmatics (77, 97, 98). This not only places strain on the child, but also on the family as awakenings are linked to a decrease in parental mood and an increase in perceived parenting hassles (99).

SIGNIFICANCE OF WHEEZE ON SLEEP QUALITY

Wheezing caused by NA correlates to an increase in the symptoms associated with disturbed sleep in both adults and children (100). Wheezing children are two

times more at risk of having difficulties falling asleep and five times more likely to have restless sleep than non-wheezing children (100). In accordance, wheezing children are nearly four times more at risk of having daytime sleepiness than non-wheezing children (100). Importantly, children with nocturnal wheeze reported a higher number of nocturnal awakenings with a corresponding increase in daytime sleepiness as compared to non-wheezing controls (101). This underscores the importance of wheeze detection as a tool to monitor sleep-related behavioral problems in children.

EFFECT OF NOCTURNAL ASTHMA ON CHILDHOOD DEVELOPMENT

Children with NA report a higher incidence of disturbed sleep-associated symptoms such as vasomotor and memory deficits, depression, anxiety and daytime sleepiness (2). A study of over 100,000 children, ages 0-17, found a significant correlation between asthma and developmental, emotional, and behavioral problems (102). It can be assumed from studies documenting the rates of undiagnosed NA in the general pediatric population that a significant proportion of the population studied suffered from NA (6, 103). Further contributing to the education problems of child NA sufferers, Diette et al. noted children with awakenings due to NA had a greater number of school absences with parents having an increased number of missed work-days (104).

CONCLUSIONS

Children with NA are not suitably monitored and thus are not receiving adequate care (87). Untreated NA leads to both negative physical and developmental consequences in children. Patient-centered measures for a child's asthma control are vital for improved asthma management (105). Proper asthma control requires patients and physicians to be familiar with NA symptoms. An automated wheeze detection device allows objective measurement of an important NA symptom that is correlated to reduced morning spirometry values. A low-cost wheeze detection device to identify and monitor NA is especially important in lower socioeconomic environments where health care access is limited, asthma rates are higher and parental reports of symptoms less reliable than more affluent areas. Additionally, detection of nocturnal wheeze in children will aid in the diagnosis and monitoring of numerous other respiratory pathologies. Future studies should analyze the appropriateness and cost/benefit of nocturnal wheeze detection for NA identification and asthma control.

ACKNOWLEDGEMENTS

The author wishes to acknowledge Dr. Noam Gavrieli for his encouragement in submitting this paper.

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