

Association between Asthma and Primary Nocturnal Enuresis in Children

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Purpose: Enuresis, sleep respiratory disorders and asthma compromise the quality of sleep in children and may occur in association with each other. An association between sleep respiratory disorders and enuresis has already been demonstrated. According to united airways disease abnormalities of the upper and lower airways may coexist. A child who wheezes has a greater chance of snoring and having obstructive sleep apnea. Since asthma and sleep respiratory disorders may be associated, and sleep respiratory disorders are associated with enuresis, we determined the possibility of an association between asthma and enuresis.

Materials and Methods: Between August 20 and March 2015 parents/guardians of children 6 to 14 years old from 16 elementary schools in our area were randomly chosen for study. Children with nonmonosymptomatic enuresis and urological or neurological disease were excluded. The Tucson and ISAAC (International Study of Asthma and Allergies in Childhood) questionnaires were used to assess sleep respiratory disorders and asthma, respectively.

Results: A total of 523 children (283 males and 240 females) with a mean $\pm$ SD age of 9.42 ± 2.46 years were included in analysis. The overall prevalence of enuresis was 15.87% (95% CI 12.98–19.26). Asthmatic children with wheezing in the last 12 months were 2.33 times more likely to have had enuresis at some point in life (OR 2.33, 95% CI 1.37–3.95, $p = 0.0017$). If enuresis was present, the chance increased to 2.78 (95% CI 1.38–5.61, $p = 0.0041$). Enuretic children were 5.34 times more prone to have apnea reported by parents (95% CI 2.19–13.03, $p = 0.0002$).

Conclusions: These findings demonstrate that asthma as well as sleep respiratory disorders is associated with primary nocturnal enuresis.

Key Words: urinary bladder, nocturnal enuresis, asthma, apnea, sleep

Abbreviations and Acronyms

OSA = obstructive sleep apnea
SRD = sleep respiratory disorder

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ENURESIS, sleep respiratory diseases and asthma compromise the quality of sleep and may occur alone or in association with each other.

Enuresis is involuntary loss of urine during sleep in children older than 5

years whose bladder control should already be fully functional.¹ Enuresis develops in 15% to 20% of 5-year-old children and these enuretic patients become continent at a rate of 15% per year.² Since approximately 10% of

children older than 7 years have at least 1 episode of nocturnal enuresis per month and about 5% of pediatric patients wet the bed once per week or more often, enuresis is considered one of the most common sleep disorders in pediatrics.³

SRDs are common childhood problems that are often not recognized. They occur due to partial and prolonged obstruction of the upper airway and/or intermittent and complete nocturnal blockage of the pharynx, leading to a change in ventilation and sleep continuity. The term SRD includes snoring and OSA among others.⁴ Epidemiological studies using questionnaires show a prevalence of 10% to 27.6% of habitual snoring and 0.5% to 9% of apnea reported by parents.⁵⁻⁷

Nocturnal asthma is not an entity distinct from bronchial asthma. Rather it is associated with greater severity and fatality of the disease. Asthma tends to worsen at night, probably as a result of an increased inflammatory response of the lower airways and bronchial hyperresponsiveness.⁸ The increase in nocturnal asthma symptoms is associated with lack of control of this condition.

The association between enuresis and SRD has been reported.⁹⁻¹¹ Most studies describe a resolution rate of approximately two-thirds or more of cases of enuresis after surgical procedures.^{9,12,13} The prevalence of enuresis in SRD correlates with the intensity of obstruction of the upper airways.¹⁴ Children who snore habitually have a higher prevalence of enuresis than those who do not snore.^{15,16}

Several mechanisms have been proposed to explain the association between SRD and asthma. Regarding snoring or apnea, repeat stimulation of the neural receptors at the entrance of the glottis and in the larynx can lead to bronchoconstriction.¹⁷ Likewise asthma may trigger symptoms of SRD due to the Venturi effect, in which the increase in air speed leads to a reduction in transmural pressure and consequent narrowing of the pharyngeal airway.⁸

Assuming that asthma is associated with SRD and this has already been correlated with enuresis, we questioned the possibility of an association between asthma and enuresis.

MATERIALS AND METHODS

We performed an observational cross-sectional study using questionnaires administered to parents/guardians of schoolchildren between 6 and 14 years old in public and private primary schools in our area. The institutional human research ethics committee approved this study and all parents/guardians of the children signed an informed consent form.

Of the 20 public and private schools that were randomly selected 16 agreed to participate. Contact with parents/guardians to complete the questionnaire was performed in 2 ways, including 1) randomly selecting 2 primary school

classes and sending a letter to the parents/guardians explaining about the project and 2) directly contacting parents/guardians as they were picking up or taking children to school, or during parent-teacher meetings.

School children younger than 6 or older than 14 years, those on diuretic medications and those with any medical condition that may involve enuresis, such as urinary tract or neurological disorders, were excluded from study.

After explaining the study to parents/guardians and applying the informed consent form an interview was scheduled. The questionnaires were then administered by telephone interviews performed by the investigator or a properly trained medical student. A structured questionnaire was used to collect general data related to child health, presence of diseases, use of medications and history of current or past bedwetting problems, allowing us to identify patients with exclusion criteria. When subjects had a history of current or past enuresis, a structured questionnaire about bedwetting was administered to classify the condition and assess the presence of associated daytime symptoms as well as current or previous treatment (see figure).

All parents/guardians answered a validated questionnaire on SRD.^{5,18} The questionnaire consisted of 13 questions about the symptoms of SRD. Possible answers were never, rarely, frequently, almost always and don't know. OSA was considered present when the parent/guardian answered frequently or almost always to the question, "Does your child stop breathing during sleeping?" "Do your child's lips ever turn blue or purple while he/she is sleeping?" or "Do you ever shake your child during sleep to make him/her breathe again?"

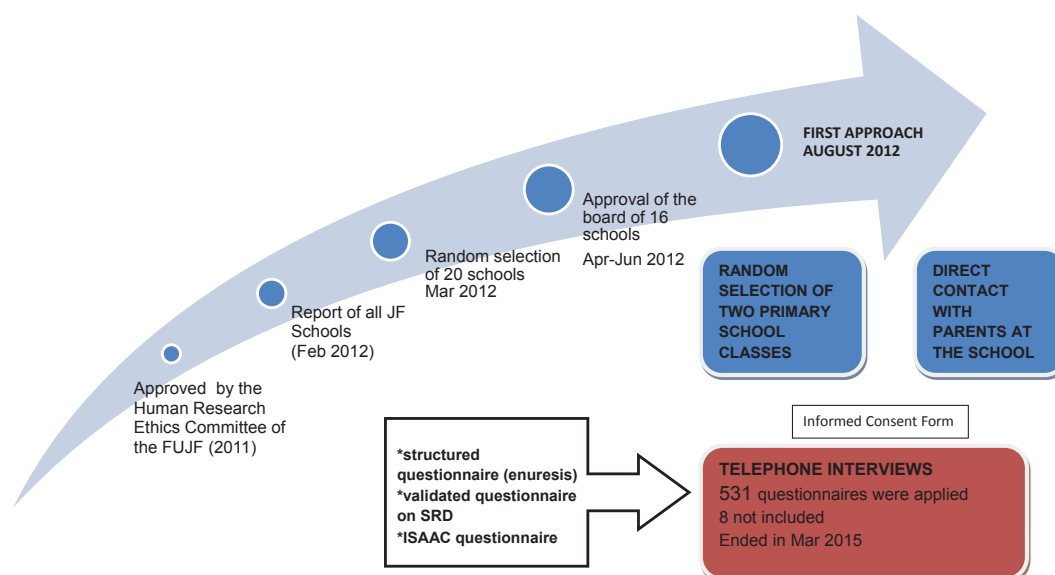
Finally, the ISAAC questionnaire was administered. This questionnaire assesses data on the current and previous history of children regarding asthma and atopy.^{19,20}

Wheezing was classified as wheezing at some point in life when the parent/guardian answered yes to the question, "Has your child ever had wheezing or whistling in the chest at any time in the past?" Wheezing was classified as wheezing in the last 12 months (current asthma) when the parent/guardian answered yes to the question, "Has your child had wheezing or whistling in the chest in the last 12 months?"

Quantitative, continuous or ordinal variables are described in regard to the central trend using the mean or median and to dispersion measures using the SD, IQR or minimum and maximum. Nominal or qualitative variables are expressed according to absolute values, percents or proportions. When comparing differences in continuous variables, the Student *t*-test, the Mann-Whitney test or ANOVA was used. To compare categorical data the Fisher exact or chi-square test and variations were used. The magnitude of associations between study parameters is expressed as the OR. The CI was used as a measure of precision and $p < 0.05$ was considered statistically significant. Prism®, version 5.0.3 was used for analysis.

RESULTS

Of the 20 public and private schools randomly selected to participate in the study 3 private schools and 1 state school refused to participate.



Project execution schedule. *FUJF*, Federal University of Juiz de Fora. *JF*, Juiz de Fora.

Eight of the 531 questionnaires administered were not included in analysis. Five children were outside the age range, although they attended elementary school. Another 3 children had medical conditions involving urinary and neurological changes such as myelomeningocele or urethral malformation.

Of the remaining 523 questionnaires 331 of contacts (63.3%) were made through a direct approach when students arrived or were picked up at school, or during parent-teacher meetings. Another 192 contacts (36.7%) were made by sending a letter to the parents/guardians of children in the 2 randomly selected classes of the participating school. Of the questionnaires 125 (23.9%) and 398 (76.1%) were received from parents/guardians of children from private and public schools, respectively.

Average age of the subjects was 9.42 ± 2.46 years. Of the subjects 45.88% were girls and 54.12% were boys.

The prevalence of enuresis at some point in life was 15.87% (95% CI 12.98–19.26). The prevalence of current enuresis, that is enuresis at the time that questionnaires were collected, was 7.27% (95% CI 5.19–9.84). The prevalence was 52.58% (95% CI 48.30–56.83) for wheezing at some point in life, 18.74% (95% CI 15.62–22.31) for current asthma (wheezing in the last 12 months) and 4.02% (95% CI 2.61–6.09) for apnea reported by parents (table 1).

A child with a history of wheezing at some point in life was 1.63 times more likely to have had enuresis at some point in life (OR 1.63, 95% CI 1.0076–2.6443, $p = 0.0465$). Such a child was 1.80 times more likely to have enuresis (OR 1.80, 95% CI 0.9036–3.6165, table 2).

Asthmatic children (wheezing in the last 12 months) were 2.33 times more likely to have had enuresis at some point in life (OR 2.33, 95% CI 1.3748–3.9536, $p = 0.0017$). If enuresis was present, the chance increased to 2.78 times more likely (95% CI 1.3831–5.6069, $p = 0.0041$, table 2). Asthmatic children between ages 6 and 10 years were more likely to have current enuresis (OR 3.023, 95% CI 1.403–6.516, $p = 0.0047$) than asthmatic children between ages 11 and 14 years (OR 1.093, 95% CI 0.126–9.465, $p = 0.9354$, tables 3 and 4).

Children whose parents/guardians reported apnea were more likely to have bedwetting at any time of life (OR 5.34, 95% CI 2.1904–13.0306, $p = 0.0002$). They were also more prone to have current enuresis (OR 4.44, 95% CI 1.5319–12.8762, $p = 0.006$, table 2).

DISCUSSION

The 7.27% prevalence of current enuresis in this study is similar to the 8% found by Nevés et al in a study using questionnaires given to parents/guardians of schoolchildren 6 to 10 years old.²¹

The prevalence of a history of wheezing (wheezing at some point in life) was 52.58% while

Table 1. Prevalence

	% Prevalence (95% CI)
Enuresis:	
At some point in life	15.87 (12.98–19.26)
Current	7.27 (5.19–9.84)
Wheezing at some point in life	52.58 (48.30–56.83)
Current asthma	18.74 (15.62–22.31)
Parent reported apnea	4.02 (2.61–6.09)

Table 2. Associations

Enuresis	OR (95% CI)	p Value
At some point in life:		
Wheezing at some point in life	1.6323 (1.0076–2.6443)	0.0465
Current asthma	2.3314 (1.3748–3.9536)	0.0017
Parent reported apnea	5.3425 (2.1904–13.0306)	0.0002
Current:		
Wheezing at some point in life	1.8077 (0.9036–3.6165)	0.0943
Current asthma	2.7847 (1.3831–5.6069)	0.0041
Parent reported apnea	4.4413 (1.5319–12.8762)	0.006

current asthma (wheezing in the last 12 months) was found in 18.74% of subjects. Considering that almost 50% of children have at least 1 episode of wheezing early in life and asthma does not develop, the variable current wheezing is considered more specific than the variable wheezing at some point in life to define asthma in the 6 to 14-year-old schoolchild.²²

According to results from a multicenter study using the ISAAC questionnaire the average prevalence of asthma in our country was 24.3% (range 16.5% to 31.2%) in children and 19% (range 11.8% to 30.5%) in adolescents.²⁰ The prevalence is similar to the prevalence found in our study.

The association between enuresis and apnea reported by parents/guardians corroborates previous studies.^{10,11} In the current series children with apnea reported by parents/guardians were at 4.44 times more risk for current enuresis than children with no history of apnea. When the history of enuresis was considered, the chance increased to 5.34 times. Previous studies show an association between enuresis and SRD in a different way. Most studies were performed at specialized otorhinolaryngology clinics where patients with symptoms such as obstruction of the upper airway are treated. The prevalence of enuresis was evaluated in these patients. A prevalence of enuresis between 22% and 42% was described in patients with symptoms of OSA.^{11–14} Symptoms of obstruction of the upper airway in enuretic patients was described in only a few studies as between 30.7% and 65.6%.^{9,10,23}

Associations between asthma and enuresis, especially between current asthma and current enuresis, are extremely important. In a demographic study performed in 2002 Rawashdeh et al

Table 4. Association between enuresis and asthma by age range

Current Asthma (yrs old)	Current Enuresis	
	OR (95% CI)	p Value
6–10	3.023 (1.403–6.516)	0.0047
11–14	1.09 (0.126–9.465)	0.9354

described the association between enuresis and wheezing at some point in life as well as a history of allergy confirmed by skin tests.²⁴ However, to our knowledge the association between enuresis and current asthma has not been reported previously.

After dividing the 523 children into 2 age groups we observed that the association between current asthma and current enuresis was stronger in younger children (6 to 10 years old). However, only 3 children had concomitant asthma and enuresis in the age range above 10 years.

Enuretic patients with OSA benefit from surgical treatment of blockage of the upper airway.^{9,11–14,23} Resolution of OSA also improves symptoms of asthma when both diseases coexist.¹⁷ One might wonder whether treating asthma in enuretic patients would have some influence on urinary symptoms or whether simple resolution of obstruction of the upper airway in patients with asthma and OSA would be decisive in putting an end to enuresis.

The recent study by Kovacevic et al shows that in most patients undergoing surgical procedures to treat obstruction of the upper airway enuresis is not resolved.²⁵ The investigators associated resolution of urinary symptoms with the preoperative severity of OSA but were unable to identify clinically significant differences between the group responsive to the surgical procedure and the unresponsive group. However, the history of bronchial asthma or other allergies was not evaluated in the study.

There is no doubt that bedwetting, SRDs and asthma share mechanisms of sleep disorders and/or disorders of awakening. The release of brain natriuretic peptide after distention of the cardiac atrial wall due to increasing negative intrathoracic pressure in upper respiratory obstruction increases sodium and water excretion, and also inhibits the release of vasopressin by the renin-angiotensin-aldosterone system.^{16,24} Patients with enuresis have increased brain natriuretic peptide and these levels are even higher in children with SRD associated with enuresis.²⁶ Other mechanisms have been suggested to explain the association between SRD and enuresis. There is a decrease in the awakening stimulus response caused by SRD, which can lead to bedwetting, and the micro-recurrent awakenings caused by obstruction of

Table 3. Current enuresis and asthma by age group

Age Group (yrs)	No. Current Asthma (%)	No. Current Enuresis (%)
Study:		
6–10	72 (13.77)	32 (6.12)
11–14	26 (4.97)	6 (1.15)
Control:		
6–10	266 (50.86)	305 (58.32)
11–14	159 (30.4)	180 (34.41)

the upper airways lead to an increased threshold of awakening and stimulation such as bladder filling or contractions of the detrusor muscle become ineffective.²⁷ Patients with obstruction of the upper airways who do not awaken to void before surgery start to awaken to urinate after surgical treatment.²⁸

Similarly asthma tends to worsen at night due to the increased inflammatory response of the lower airways as well as an increase in bronchial hyper-responsiveness. Pulmonary function measurements such as FEV1 (forced expiratory volume in 1 second) and PEF (peak expiratory flow rate) are at a minimum at 4 a.m.⁸ Nocturnal asthma can induce blockage of the upper airway due to the Venturi effect⁹ while SRD may lead to bronchoconstriction due to repeat stimulation of neural receptors near the pharynx and glottis.¹⁷

Whether the association between asthma and enuresis found in our study depends exclusively on coexistence of obstruction of the upper airway is not known. The stronger association between bed-wetting and current asthma in children younger than 10 years in our study can correlate to OSA coexistence, which is more common in younger children. The limited number of patients (3) older than 10 years with concomitant asthma and

enuresis made a comparison between the 2 age ranges difficult.

The limitations in the current study are common to all surveys performed through questionnaires, such as a high rate of refusal, especially when trying to contact families by letter, which showed a 75.8% rate. Assessment of sleep apnea in children by questionnaires instead of by polysomnography may interfere in determining the incidence since many parents may not accurately know about their child's sleep. However, the prevalence that we found is in accord with the literature.

Notably there are gaps in the approach to enuretic patients with respiratory symptoms. None of the mechanisms mentioned explains the association between enuresis and the history of allergy confirmed by skin tests.²³

Further studies are needed to assess the clinical profile of patients with enuresis associated with asthma as well as that of patients with OSA and enuresis in whom bedwetting does not improve after surgical treatment of upper respiratory obstruction. In conclusion, because children with asthma as well as obstructive apnea are at a higher risk for enuresis, investigation of respiratory symptoms should be done when evaluating enuretic children.

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