

Obstructive sleep-disordered breathing, enuresis and combined disorders in children: chance or related association?

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Summary

Nocturnal enuresis is usually diagnosed and treated by a primary paediatrician or family practitioner; if there is any doubt, the children may be referred to a paediatric urologist. Obstructive sleep-disordered breathing is a complex, multifactorial disorder. Adenotonsillar hypertrophy is considered an important factor associated with obstructive sleep apnoea syndrome. Enuresis and obstructive sleep-disordered breathing are both frequent problems of sleep in childhood. We conducted an electronic search in Medline, Scopus and the ISI Web of Science to look for published material and identify a putative link between nocturnal enuresis and obstructive sleep-disordered breathing. A total number of 98 documents were found, but 24 of these had to be excluded after an attentive reading of the title, abstract or full text because the information therein was not suitable for the aims of our search.

Studies have found that children with obstructive sleep apnoea syndrome frequently also have nocturnal enuresis. Both disorders have an underlying sleep disturbance characterised by an altered arousal response and sleep fragmentation. The pathophysiology of enuretic events is seemingly linked to nocturnal obstructive events, causing increased intra-abdominal pressure and altered systemic blood pressure that induces natriuresis and polyuria by altering levels of antidiuretic hormone, and atrial and brain natriuretic peptides. We found 17 studies regarding the urological outcome of treatment for obstructive sleep-disordered breathing in children with enuresis. Although a vast amount of information is now available regarding the relationship between nocturnal enuresis and obstructive sleep-disordered breathing, many of the published studies were uncontrolled, retrospective or prospective cohort studies (grade C recommendation). Resolution of enuresis after medical or surgi-

cal treatment for obstructive sleep-disordered breathing has been emphasised. Consequently, symptoms such as snoring, sleep apnoeas and restless sleep should be sought for all children with enuresis. Confirmed obstructive sleep-disordered breathing should be treated promptly; subsequently, the persistence of enuresis requires treatment following the standard protocol.

Key words: *obstructive sleep apnoea syndrome; sleep-disordered breathing; enuresis; children*

Abbreviations:

ADH: antidiuretic hormone

ADHD: attention-deficit hyperactivity disorder

ANP: atrial natriuretic peptide

BNP: brain natriuretic peptide

HRQoL: health-related quality of life

OSAS: obstructive sleep apnoea syndrome

SDB: sleep-disordered breathing

Introduction

Sleep-disordered breathing

Obstructive sleep-disordered breathing (SDB) is a syndrome of upper airway dysfunction that occurs during sleep and is characterised by snoring and/or increased respiratory effort. Obstructive sleep apnoea syndrome (OSAS) is characterised by witnessed apnoea, unrefreshing sleep and excessive daytime sleepiness [1]. The prevalence of OSAS is approximately 0.7 to 3% in children [2–5]. The first peak occurs in children between 2 and 8 years of age and the second peak during adolescence [6]. A follow-up study has shown that only 12% of children aged 5 to 9 years had OSAS resolution at 7 months of follow-up without treatment [7]. A summary of the age-related prevalence of childhood OSAS is shown in figure 1.

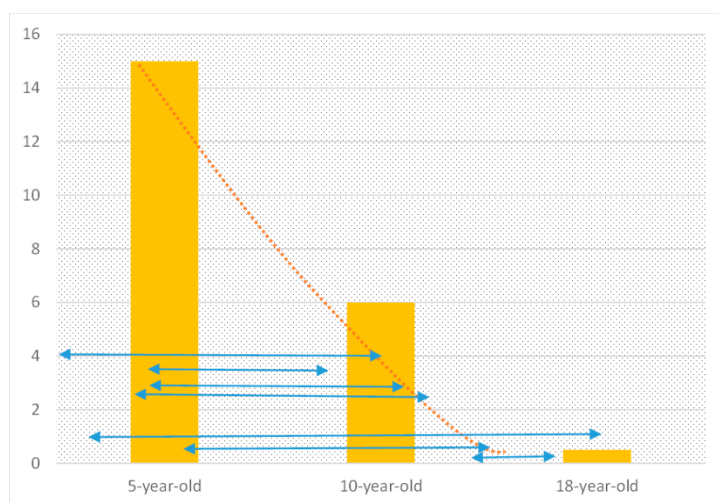


Figure 1

Prevalence of age-related enuresis – yellow rectangle [8, 9], and parent-reported sleep apnoea from various Western countries – blue line [4].

OSAS is a complex, multifactorial disorder. Adenotonsillar hypertrophy is considered an important factor associated with OSAS [10, 11]. Accordingly, adenotonsillectomy can achieve a significant improvement in the severity of obstructive SDB [12]. Other factors are linked to characteristic facial features [13–17]. Correction of craniofacial deformities in children with malocclusion has been shown to improve OSAS [18]. Other putative factors include ethnicity (African-American), prematurity and Down's syndrome [19], obesity [20, 21], and craniofacial anomaly in syndromic patients (achondroplasia) [22]. In a recent multicentre retrospective study [12], children with chronic asthma were found to be at higher risk of residual OSAS.

OSAS results in snoring, episodic oxyhaemoglobin desaturation, hypercapnia and sleep disruption [11, 23]. Snoring in children has been associated with cortical arousal [24] and multiple neurobehavioural consequences [25–29]. OSAS children have significantly greater morbidity [30]. Children with SDB can have a dolico facial pattern [31] and rhinosinus involvement [32]. They frequently experience decreases in mean neuronal metabolites in the left hippocampus [33], a reduction of middle cerebral artery blood flow velocity [34], prefrontal cortex dysregulation [35], grey matter density deficit in prefrontal regions, reduced attention and visual fine-motor coordination scores [36], and a blunted daytime cerebral blood flow response to hypercapnia [37]. Possible consequences include deficits in Intelligence Quotient and executive functions [35, 38], daytime sleepiness [39, 40], impairment of health-related quality of life (HRQoL) [41, 42], increased internalising (over-control of emotions) and externalising symptoms (interpersonal relationships) [43], psychosocial, cognitive and behavioural impairments [44, 45] that persist even with OSAS resolution [46], poorer academic performance [47] – not yet detected at preschool age [48], periodic limb movements [49] and exacerbation of attention-deficit hyperactivity disorder (ADHD) [50, 51]. An improvement in behaviour, cognitive function, and quality of life has been frequently observed following adenotonsillectomy [52–56]. Autonomic activation from frequent cortical arousal has been reported [57–59]. The respiratory events trigger a greater acute cardiovascular response, including surges in blood pressure and heart rate [60–62], altered cardiovascular and hemodynamic function [63], and an alteration of both antidiuretic hormone (ADH) and brain natriuretic peptide (BNP) levels [64]. A significantly higher value of oxidative stress markers has also been observed in children

with SDB [65] along with a higher intra-ocular pressure level [66].

Nocturnal enuresis

Nocturnal enuresis is a complex disorder characterised by intermittent incontinence that occurs exclusively during sleep. Nocturnal enuresis is applicable to children who are at least 5 years old [67]. There are two subtypes, monosymptomatic nocturnal enuresis and non-monosymptomatic nocturnal enuresis, depending on the absence or presence of symptoms of lower urinary tract and bladder dysfunction [67]. Primary nocturnal enuresis applies to children who have not had a previous dry period for at least 6 months [68]. Secondary nocturnal enuresis refers to children who have had a previous dry period of >6 months [67]. Nocturnal enuresis is one of the most common problems in childhood, with a prevalence of between 2 and 15% [67, 69–71]. The overall prevalence of nocturnal enuresis declines with increasing age, from 15% in 5-year-old children to 0.5% in those aged ≥ 18 years [8, 9], with an annual healing rate of approximately 15% [72, 73]. A summary of the prevalence of childhood nocturnal enuresis is shown in figure 1.

Although several aetiologies have been proposed for nocturnal enuresis [74, 75], a clear pathogenesis remains mostly unknown [76]. Reduced functional bladder capacity [77], detrusor overactivity [78–80] and elevated arousal thresholds [78, 81, 82] have been implicated. Butler et al. proposed a three-system model that lists excessive nocturnal urine production, nocturnal bladder overactivity and failure to awaken in response to bladder sensation as underlying factors [69, 83]. Abnormal function of the autonomic nervous system [84–87] and the central dopaminergic pathways [88] may alter the control of bladder function. Moreover, nocturnal polyuria [89–91] due to decreased ADH release has also been reported [92–94]. Children with nocturnal enuresis may have decreased ADH secretion [95, 96] and higher BNP values [97] during sleep. Circadian variations [98] may be involved in the impaired regulation of water and electrolytes, micturition, and bladder capacity [93, 99].

Sleep problems in children with enuresis have been studied for a long time. Immaturity of the sleep mechanism has been proposed as a cause [100]. Previously, sleep differences between children with nocturnal enuresis and their dry peers were not clearly and consistently observed [86, 100–104]. The enuretic event was found to be a predominantly non-rapid eye movement (non-REM) sleep phenomenon,

with bladder voiding occurring at any stage of sleep and throughout the night [82, 100, 105–107]. Recent observations have shown that children with nocturnal enuresis have disturbed sleep [108, 109]. In particular, they have increased deep sleep, higher arousal thresholds and daytime sleepiness [81, 108–111], sleep fragmentation, frequent cortical arousals [78, 89, 111], and periodic limb movements [89, 110, 112]. High arousal thresholds have been considered one of the leading causes of nocturnal enuresis. Deep sleep prevents arousals when the bladder is full [75, 81, 113]. Sleep fragmentation leads to sleep deprivation, thus affecting endocrine, metabolic, immune, inflammatory and cardiovascular regulation [87, 114].

Several studies have confirmed that children with nocturnal enuresis have low HRQoL [111, 115–117]. Behavioural disorders affect 20 to 40% of children with nocturnal enuresis [118]. They have higher levels of daytime sleepiness [111], daytime internal and external behaviour problems and impaired neuropsychological functioning [83, 119–122]. Nocturnal enuresis generates significant impairment of self-esteem [123] and an impaired HRQoL that worsens over time [117, 124]; their mothers also have lower quality-of-life scores [125]. In these children, periodic limb movements during sleep are associated with a lower HRQoL [126]. They frequently display an ADHD pattern [127–130] and develop conduct disorders [131]. In children with monosymptomatic nocturnal enuresis, magnetic resonance imaging revealed substantial structural abnormalities in the thalamus, medial frontal gyrus, anterior cingulate cortex and insula, which are involved in the micturition control network [132].

Aims of the review

Practical consensus guidelines for the management of primary nocturnal enuresis do not mention [133], or mention only marginally, SDB in children with nocturnal enuresis, particularly in those who have treatment resistance and comorbidities [67, 134]. Subjects with habitual snoring are at greater risk of primary nocturnal enuresis than those without snoring, regardless of OSA severity [135]. Therefore, the aims of this paper were to look for published material and to possibly find a putative link between nocturnal enuresis and SDB. In particular, we were trying to answer the following questions:

1. Is there a link between enuresis and upper respiratory obstruction?
2. What is the frequency of OSAS in enuretic children?
3. Why does OSAS in children increase the risk of enuresis?
4. Can treatment of OSAS resolve enuresis?

Methods

We conducted an electronic search in Medline (with PubMed interface), Scopus and the ISI Web of Science using ["sleep disordered breathing" OR "sleep apnea"] AND "enuresis" AND "children" in title/abstract/keywords for relevant articles in English. The studies on children with genetic diseases (e.g., achondroplasia), or neurological and endocrinological (e.g., growth hormone deficiency) conditions were excluded. All the articles that were retrieved by our search criteria were systematically reviewed by two authors (MZ and LN).

The bibliographies of the selected articles were also examined to identify other pertinent articles.

Firstly, we looked for studies that aimed to answer our four questions (see above) Regarding the fourth question, we looked for studies on the outcome of treatment for obstructive SDB in children with enuresis according to the PRISMA guidelines [136]. We also examined the strength of the evidence (grade of recommendation) according to the Oxford Centre for Evidence-Based Medicine (2011) and the Centre for Evidence-Based Medicine (2009).

Results

A flow chart of our criteria and results are summarized in figure 2. A total of 181 published articles were found; 98 of these were assessed for eligibility, but 24 of them had to be excluded after an attentive reading of the title, abstract and/or full text because the information did not concern the four questions that were the basis of our research. Finally, we found 17 studies regarding the urological outcome of treatment for obstructive SDB in children with enuresis.

Is there a link between enuresis and upper respiratory obstruction?

The possible relationship between nocturnal enuresis and obstructive SDB was reported nearly 40 years ago [137–139]. The prevalence of nocturnal enuresis among children with upper airway obstruction was found to be high [140–142], particularly in those not responding to standard treatment with desmopressin and/or an alarm [143]. Several studies have associated childhood nocturnal enuresis with coexistent obstructive SDB [141, 142, 144–147], particularly in children who also have daytime incontinence [148]. Moreover, patients with refractory nocturnal enuresis have a significantly higher prevalence of OSAS, with no difference between sexes [149]. In only one study was the association found only in girls [150]. Facial pattern (dolico-facial) and abnormal head posture was observed in children with nocturnal enuresis, features closely linked to OSAS [151].

Children with nocturnal enuresis and OSAS had a higher arousal index than enuretic children without OSAS [152]. Therefore, the prevalence of nocturnal enuresis could not be directly related to severity of OSAS [141, 152]. The presence of both upper airway narrowing and nocturnal enuresis exhibited the highest sensitivity for detecting children with OSAS [153]. Overweight and monosymptomatic nocturnal enuresis have been associated with OSAS, but not with each other [154]. Nocturnal enuresis has been significantly associated with the presence of moderate-to-severe OSAS in a fully adjusted model considering tonsillar hypertrophy, obesity, gender and age [155]. Residual OSAS after surgery has been significantly associated with coexistent nocturnal enuresis [156].

The most important symptoms and signs – breathing through the mouth, tonsillar size and nasal congestion – correlated with nocturnal enuresis in children who do not respond to standard treatment [152]. Children with therapy-resistant enuresis and without a history of snoring or sleep apnoea showed subclinical signs of disordered respiration, respiratory arousals and a high frequency of hypopnoeas [157].

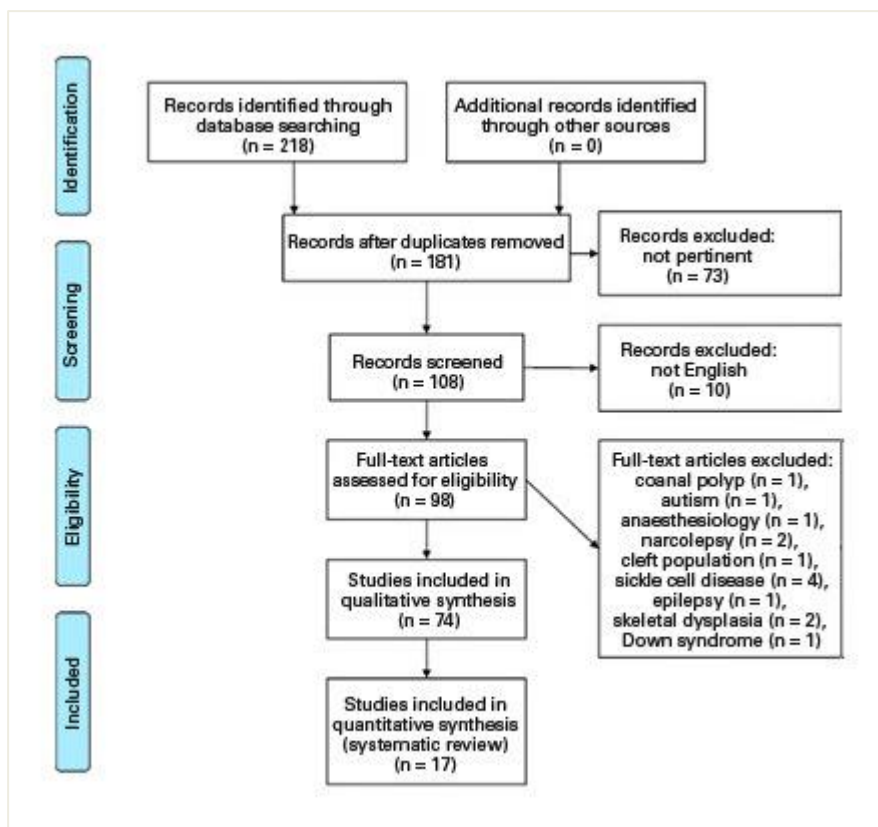


Figure 2

Search criteria for relevant articles and results.

The frequency of nocturnal enuresis is also greater in children with habitual snoring [97, 152, 158–160]. Snoring in children with monosymptomatic nocturnal enuresis increases their risk of behavioural and psychosocial problems, with impaired HRQoL [161]. Nocturnal enuresis and obstructive SDB, ranging in severity from snoring to OSAS, have both been associated with impaired HRQoL [117, 119, 161]. HRQoL was found to be similar between children with obstructive SDB, with and without enuresis, thus suggesting that the presence of SDB, rather than the presence of nocturnal enuresis, is the major contributing factor to HRQoL impairment [64]. Excessive autonomic activation, hyperactive behaviour and enuresis during sleep have been reported in children with symptoms of obstructive SDB [26].

What is the frequency of OSAS in enuretic children?

SDB is frequent in children with monosymptomatic nocturnal enuresis [143, 148]. More specifically, nocturnal enuresis has been reported in 8 to 47% of children with obstructive SDB [141, 143, 162–164]. Recently, of 87 children (aged 9.5 ± 2.6 years) out of 140 enuretic participants in a prospective study who underwent polysomnography, 6 were diagnosed with severe apnoea, 40.7% had mild/moderate apnoea; a family history of nocturnal enuresis and constipation were both extremely frequent. The authors suggested a multidisciplinary approach of the problem [165].

Complete resolution of nocturnal enuresis has been reported in 31 to 76% of OSAS children within months of surgical intervention [9, 166]; interestingly, in about half of them nocturnal enuresis disappeared within 1 month [167, 168]. Spontaneous resolution of nocturnal enuresis has been used to explain nocturnal enuresis remission after adenotonsillectomy [167, 169]. Compared with the 15% annual rate of spontaneous resolution, this resolution rate after surgery

should be considered significantly higher than expected [72, 170].

Why does OSAS in children increase the risk of enuresis?

Children who wet the bed are more difficult to arouse from sleep than children who do not [106]. Obstructive SDB may promote nocturnal enuresis by decreasing the arousal response [171], but whether decreased arousal response contributes to both OSA and nocturnal enuresis is questionable [110, 142, 172, 173]. Daytime urodynamics are similar in children with and without nocturnal enuresis [174]. Therefore, increased intra-abdominal pressure caused by respiratory efforts against an obstructed airway has been implicated in the pathogenesis of nocturnal enuresis because of increasing bladder pressure [175].

Urinary excretion of sodium and diastolic blood pressure have been found to increase in parallel with the severity of obstructive SDB [176]. At the end of nocturnal obstructive events, repetitive increases in systemic blood pressure occur, and these can lead to pressure-induced natriuresis [177, 178]. On the contrary, natriuresis and polyuria are completely suppressed by effective treatment of OSAS [70, 144].

SDB can affect the secretion of urinary hormones such as atrial natriuretic peptide (ANP) and ADH. Nocturnal increase in ANP and a decrease in ADH are responsible for the nocturnal diuresis and natriuresis associated with OSA. It has been observed that adults with OSAS have elevated ANP and decreased levels of ADH [179–181], and the normal nocturnal decrease in urine output does not occur [182–184]. ADH normalises after adenotonsillectomy [183]. In patients with OSA, plasma ANP is negatively correlated with cumulative apnoea duration and lowest arterial oxygen saturation (SaO_2), whereas a positive correlation has been observed

with the highest change in intrathoracic pressure [179]. Upper airway obstruction leads to negative intrathoracic pressure swings, increases systemic venous return, generates high preload at the right ventricle and ultimately enhances the left cardiac ventricle afterload [185, 186]. Acute overload of the cardiac ventricles may promote the release of ANP from ventricular myocytes, which then induces vasodilation and natriuresis [187]. nocturnal enuresis may eventually be triggered by sleep apnoea because an accentuated negative intrathoracic pressure during sleep leads to abnormal secretion of ANP [144].

Enuretic children with obstructive SDB displayed a greater increase in BNP values [97], which correlated with obstructive SDB severity [188]. After successful treatment of OSA-induced ANP secretion, urine output and sodium excretion

decreased, whereas renin and aldosterone values increased [179, 181, 189, 190]. Adenotonsillectomy for OSAS is accompanied by a reduction of morning venous BNP levels in childhood [191]. Significant increases in plasma ADH and significant decreases in plasma BNP were observed in all children, with no difference between responders and nonresponders to surgery for OSAS [174]. A significant increase in plasma ADH and a significant decrease in plasma BNP were also recorded after adenotonsillectomy in all children, with no difference between those who became dry and those who remained wet [192].

A summary of the putative mechanisms for pathogenesis of enuresis in patients with sleep disordered breathing is shown in figure 3.

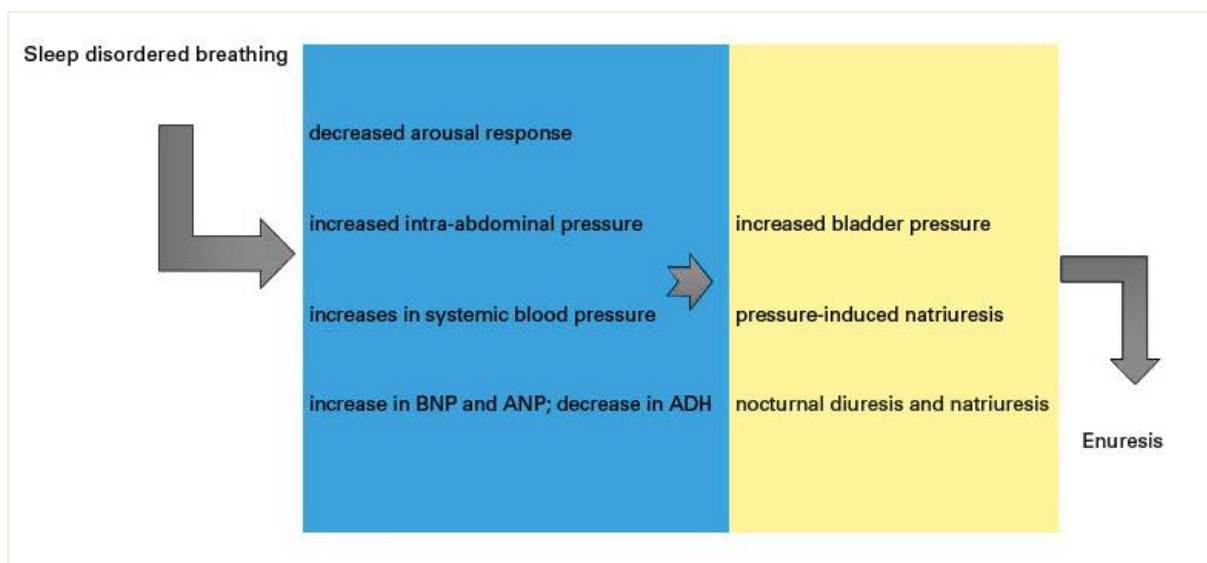


Figure 3

Putative mechanisms for pathogenesis of enuresis in patients with sleep disordered breathing
ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide

Can treatment of OSAS resolve enuresis?

A summary of the studies concerning the urological outcome of treatment for obstructive SDB in children with enuresis is shown in table 1.

Administration of nasal corticosteroids was associated with resolution of nocturnal enuresis in two children with mild obstructive SDB [193]. Moreover, tonsillectomy and/or adenotonsillectomy have been frequently associated with a high resolution rate of childhood nocturnal enuresis [9, 140, 142, 162, 166–168, 192, 194–196], although this evidence could not be confirmed in one study [169], which considered grading of tonsillar hypertrophy, but not OSAS grading by polysomnography. adenotonsillectomy significantly improved the HRQoL in all children with obstructive SDB and nocturnal enuresis, regardless of nocturnal enuresis outcomes [64].

Rapid maxillary expansion produces an immediate change in transverse dimensions of the nasal cavity, circummaxillary sutures and aperture width [199]. The positive impact of rapid maxillary expansion on respiration could possibly explain its antienuretic effect in some patients who might have a coexistent OSAS and a nocturnal respiratory

problem [157, 200]. In children with obstructive SDB and therapy-resistant nocturnal enuresis, rapid maxillary expansion may prove to be a harmless and curative therapy for both problems [148, 197, 198].

Some limitations of these studies should be addressed. In particular, none of the outcome studies were peer reviewed, randomised or quasi-randomised (e.g., controlled before-and-after studies, interrupted time series) and controlled. On the contrary, the studies were mostly retrospective/prospective/observational. The strength of an evidence analysis showed that 12 out of the 17 studies were of 2c level. Moreover, some studies (table 1) included children under 5 years old [142, 162, 167, 169, 194, 195] and the improvement in these younger children may be related to natural development.

Table 1: Urological outcome of the treatment for sleep disordered breathing in children with enuresis.					
Authors [ref.]	Population	Intervention	Outcome	Study design	Strength of the evidence (therapy)
Alexopoulos et al., 2005 [193]	8-year-old boy and 7-year-old girl with primary NE, chronic nasal obstruction, and loud snoring	Nasal budesonide	Resolution of enuresis (2–4 weeks)	Case reports	4
Firoozi F et al., 2006 [9]	86 patients; 42% with NE	A&T	12 patients (33%) had complete resolution, 11 (31%) had significant improvement and 13 (36%) showed no change	Prospective population-based study	2c
Basha S et al., 2005 [162]	326 patients aged 2–18 years over a 44-month period; 32.8% children with a positive history of enuresis of whom 53.3% agreed to participate in the second phase of the study	Tonsillectomy or adenoidectomy	61.4% of the children were free of enuresis, 22.8% had a decrease in enuresis, and 15.8% had no change in enuresis.	Retrospective chart review with prospective collection of data	2c
Cinar U et al., 2001 [140]	321 children (5–16 years), 35% had NE	A&T	64/111 were evaluated postoperatively: after 3 months. 63% were free of their complaints; 4% reported a decrease in the frequency of NE; 24/111 had no change in their complaints	Population-based study	2c
Weider DJ et al., 1991 [142]	115 children (3–19 years)	A&T	Significant decrease in or complete cure of nocturnal enuresis in 87 (76%)	Population-based study	2c
Leiberman et al., 2006 [166]	All relevant published data by the Soroka University Medical Center compared with MEDLINE linked literature	A&T	Reduction of nocturnal enuresis	Narrative (review article)	-
Weissbach et al., 2006 [167]	161 children (4–18 years of age); 42 had enuresis;	A&T	27 of these 42 underwent A&T: in 41% enuresis totally disappeared within 1 month	Retrospective review of clinical data	2c
Kovacevic L et al., 2013 [168]	417 children (5–18 years of age); 24% had NE	Tonsillectomy and/or adenoidectomy	49% responded to A&T; of these, 61% resolved within 1 month postoperatively	Observational, pilot study	2c
Kovacevic L et al., 2014 [192]	46 children (8.79 ± 2.41 years)	A&T	43.5% of patients became dry; those who became dry had more frequent arousal episodes from apnoea events	Prospective study	2c
Ahmadi MS et al., 2013 [194]	97 children aged 3–12 years	A&T	3 months after A&T, NE had resolved completely in 60.7% children and had shown relative improvement in 26.2% children	Prospective cohort study	2c
Jeyakumar A et al., 2012 [195]	14 studies, 3 550 children (18 months to 19 years) had SDB, one-third had a diagnosis of NE	A&T	Preoperative prevalence of NE was 31%; postoperative prevalence of NE was 16%	Systematic review	3a
Kalorin CM et al., 2010 [169]	326 toilet-trained children 3–15 years old; 257 in the tonsillectomy group and 69 in the control group	Tonsillectomy	Cure rates for NE and daytime incontinence at 3 and 6 months postoperatively, respectively, were 40% and 50% in the tonsillectomy group (p = 0.60), and 35% and 48% in the control group	Prospective study	2c
Kovacevic L et al., 2015 [64]	30 children in the study group vs 30 age-matched controls before and 4 weeks after T&A	T&A	Improvement was shown for HRQoL in children with both SDB and NE (study group) and children with SDB without NE (controls)	Prospective study	2c
Park S, et al. 2016 [196]	183 children (8.17 ± 2.84 years), 9.3% with NE.	A&T	After A&T, 76.5% showed complete resolution of NE	Prospective study	2c
Nevés T et al., 2014 [157]	34 children (10.7 ± 1.8 years)	Orthodontic widening of the palate	Proportions of responders, intermediate responders and nonresponders during treatment were 21.2%, 27.3% and 51.5%, respectively	Clinical trial	2c
Timms DJ, 1990 [197]	10 children (6.5–15.5 years)	RME	NE ceased within a few months of maxillary expansion	Prospective study	4
Kuroi J, Modin H, 1998 [198]	10 children (8–13 years)	RME	Within 1 month of RME of 3 to 5 mm, 4 children were completely dry and 3 showed notable imFet alprovement	Prospective study	4

A&T = adenotonsillectomy; HRQoL = health-related quality of life; NE = nocturnal enuresis; RME = rapid maxillary expansion; SDB = sleep-disordered breathing

Conclusions

Nocturnal enuresis and obstructive SDB are both frequent problems of sleep that coexist in childhood. Nocturnal enuresis is diagnosed and treated by a primary paediatrician or family practitioner; if the diagnosis is doubtful, the children may be referred to a paediatric urologist. Other studies found that children with OSAS had frequent bedwetting. Although a vast amount of information is now available regarding the relationship between nocturnal enuresis and obstructive SDB, many of the published studies were uncontrolled, retrospective or prospective cohort studies (grade C recommendation). A correlation between the two conditions is frequently reported, and resolution of nocturnal enuresis following medical or surgical treatment for obstructive SDB is emphasised. Both disorders have an underlying sleep disturbance characterised by altered arousal response and sleep fragmentation. The pathophysiology of enuretic events is seemingly linked to nocturnal obstructive events, causing increased intra-abdominal pressure, altered systemic blood pressure that induces natriuresis and polyuria by altering ADH, ANP and BNP levels. Treatment of obstructive SDB, mainly due to tonsil and adenoid hypertrophy, leads to significant resolution of nocturnal enuresis in most patients, accompanied by normalisation of ADH, ANP and BNP levels, and concomitant improvement of HRQoL.

In summary, since our information comes from observational studies, there is a need to further explore these correlations in controlled studies. In the meantime, symptoms of OSAS such as snoring, sleep apnoea and restless sleep should be sought for all children with nocturnal enuresis. Confirmed obstructive SDB should be treated promptly; the persistence of nocturnal enuresis afterwards would require treatment following the standard protocol.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

Author contributions

Study conception and design: Marco Zaffanello; Collection of data: Marco Zaffanello, Emma Gasperi, Giorgio Piacentini, Giuseppe Lippi, Vassilios Fanos; Analysis and interpretation of data: Marco Zaffanello, Giorgio Piacentini, Giuseppe Lippi, Vassilios Fanos; Drafting of manuscript: Marco Zaffanello, Giorgio Piacentini, Giuseppe Lippi, Vassilios Fanos; Critical revision: Luana Nosetti, Giuseppe Lippi, Giorgio Piacentini

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