

Relationship Between Obstructive Sleep Apnea and Enuresis in Children: Current Perspectives and Beyond

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Background: Nocturnal enuresis (NE) and obstructive sleep apnea (OSA) are common diseases in children, which often cause various social and psychological problems. The coexistence of both seriously affects the physical and mental health of children. However, whether OSA can directly lead to NE and the specific pathogenesis is still unclear. Moreover, the benefits of surgical and non-surgical treatments for OSA on NE symptoms remain controversial. This review summarizes the relationship between NE and OSA and how to treat them, aiming to provide a reference for the clinical treatment of OSA and NE in children.

Methods: All pertinent original publications to this point from PubMed database have been collected, including investigations on the connection between OSA and NE as well as studies on the mechanism and therapeutic strategy of NE in children with OSA.

Results: There is a bidirectional relationship between OSA and NE in children. NE increases with the incidence of OSA, and children with NE often have sleep-disordered respiratory disease. Children with OSA may be susceptible to NE due to aberrant humoral factors secretion, sleep-wake disorder, bladder dysfunction, obesity, and psychosomatic factors. It has been suggested that adenotonsillectomy (AT) may be the best treatment option for children suffering from OSA with NE. The benefits of positive airway pressure (PAP) therapy in children with NE remain to be further studied.

Conclusion: NE and OSA comorbidity seriously affect the physical and mental health of children. AT can benefit children with OSA and NE. A comprehensive multidisciplinary evaluation of children with NE and OSA is needed, and the mechanism and treatment of NE in children with OSA need to be further explored.

Keywords: obstructive sleep apnea, nocturnal enuresis, children, atrial natriuretic peptide, sleep-wake disorder, adenotonsillectomy

Introduction

Nocturnal enuresis (NE) and obstructive sleep apnea (OSA) are both common diseases in children.¹ Intermittent incontinence that occurs during the waking state is called daytime urinary incontinence.¹ In contrast, NE, commonly known as bed-wetting, is a special type of urinary incontinence that occurs during sleep.^{1,3} According to the International Children's Continence Society (ICCS) criteria, NE refers to the occurrence of involuntary urine leakage symptoms in children aged >5 years during nighttime sleep with a frequency >1 time/month and a duration >3 months after excluding organic causes.³ ICCS classifies NE into two types: primary and secondary NE or NE into monosymptomatic and non-monosymptomatic NE based on the absence or presence of other lower urinary tract symptoms.³ According to the latest epidemiologic studies, between 6% and 16% of children above the age of five have NE.⁵⁻⁸ A cross-sectional study from Korea showed that the prevalence of NE did not significantly decrease with age, with a prevalence of NE of up to 2.6%

aged 16–40 years.⁸ The etiology of NE is complicated, and the pathogenesis is not completely known. It is generally believed to be the result of the interaction among sleep-awakening disorder, nocturnal polyuria, bladder and urethra dysfunction, neurotransmitter and receptor abnormalities in the central nervous system, and genetic factors.^{10–13} Mental and behavioral abnormalities are often one of the adverse events caused by NE.¹³ The development of voiding control function in children depends on the increase of bladder capacity, autonomous control of the urethral sphincter, and voiding reflex.^{1,3} Any problem of them can lead to NE.

OSA in children refers to repeated airway partial or complete collapse and obstruction and disturbed sleep ventilation and sleep structure, leading to sleep hypoxia, hypercapnia, sympathetic excitation, activated oxidative stress, and inflammatory damage response.^{15–17} The clinical manifestations of OSA include snoring, breath holding, laborious breathing, mouth breathing, and awakening difficulties during sleep, which can also result in growth retardation, non-specific behavioral disorders, cognitive dysfunction, and decreased intelligence and learning.¹⁴ Polysomnography is currently the gold standard for the diagnosis of OSA in children. Apnoea–hypopnoea index (AHI) is the most commonly reported polysomnographic parameter describing OSA severity in the literatures. If the AHI detected by PSG during sleep monitoring is more than five events per hour, OSA can be diagnosed.¹⁴ The prevalence of OSA in children is 1% to 4%.¹⁵ OSA in children is commonly caused by compliance changes brought on by increased upper airway resistances, such as allergies sinusitis, laryngeal cartilaginous softness, obesity-related airway stenosis, craniofacial deformity, and similar conditions. The most frequent reason is tonsil and/or adenoid hypertrophy.¹⁶

The peak age of children with NE and OSA is 5–7 years old, and they often cause various psychosocial problems, which have serious negative effects on the life quality of children and their families.^{14,17} At present, the influence of OSA on NE has been widely concerned by scholars. Many studies have suggested that cardiopulmonary and renal reflex-induced neuroendocrine disorder may play an important role in the mechanism of NE in children with OSA, but its specific pathogenesis is still unclear.^{9,10} Moreover, the benefits of the surgical and non-surgical treatments of OSA in children with NE remain controversial. In this review, we summarized the pathogenesis and benefits of treatment of NE caused by OSA, which aimed to provide a reference for the clinical treatment of NE in children with OSA.

Methods

This study conducted an extensive search for papers published from 1981 to 2024 using the PubMed database. We use the search terms: “((Nocturnal enuresis) AND (Obstructive sleep apnea)) AND (Children)”. In order to maintain a focus on formal and significant scholarly contributions, only articles and reviews were included. Each included literature was independently reviewed and examined by at least three authors for relevance and quality to the study topic.

Results

The Association Between OSA and NE and the Severity of the Comorbidity

There is a bidirectional relationship between OSA and NE in children. The incidence of NE increases along with OSA and children with NE often have respiratory disorder disease.^{1,15} Both diseases have an underlying sleep disorder characterized by sleep fragmentation and altered wake response. Abnormal facial pattern (dolico-facial) and head posture were observed in children with NE, features closely linked to OSA.¹⁸ Using bladder manometry, researchers monitored the bladder pressure of patients throughout the night and found that arousal disorder-related symptoms such as detrusor hyperactivity, bladder instability, and increased nocturnal urination were all linked to NE.¹⁹ Subclinical symptoms of disturbed breathing, respiratory arousals, and hypopneas are often observed in children with therapy-resistant NE who have no prior history of snoring or sleep apnea.²⁰ In the recent study, 68.5% of the children with primary NE had OSA, with two-thirds having moderate-to-severe OSA (AHI \geq 5 episodes/h).²¹ Children with primary NE were at risk for the development of OSA in children with primary NE were associated with nasal obstruction due to nasal blockage, the adenoid/adult facial phenotype, and an arched palate. Without regard to gender, patients with refractory NE had a noticeably greater frequency of OSA.²² Moreover, it has been reported that children with OSA constituted about 27% of the pediatric population, and 8–47% of children with OSA had symptoms of NE, which suggests that it had an important clinical significance to ask and evaluate bedwetting for children with OSA.^{23,24} OSA is frequent in children

with monosymptomatic NE. The study by Ferrara et al found that the prevalence of sleep disorders in children with NE was high: 7% of children had sleep apnea, 41.2% had bruxism, 57.8% had snoring, 47.3% had sleep talking, and 15.7% had restless sleep.²⁵ Sleep questionnaires showed that the NE children had more sleep problems than the control group, especially breathing disorders, and daytime sleepiness.²⁶ A recent prospective study included 140 NE patients, 87 patients (aged 9.5 ± 2.6 years) underwent polysomnography, 6 of them were diagnosed with severe apnea, and 40.7% with mild/moderate apnea.²⁷ Soylu et al reported that 80% of patients with primary NE and 36% of secondary NE patients had OSA, while the frequency of primary and secondary NE for OSA children was 24% and 6%, respectively.²³ All these suggest that children with OSA and NE are a large group and need more scholars' attention. The presence of frequent partial or complete OSA can interfere with normal sleep and breathing during sleep, resulting in OSA causing a range of symptoms.¹⁴ A cross-sectional observational study of children aged 6–12 years showed that 22.3% of elementary school children had NE, and OSA was a common problem in children with NE.²⁸ For school-age children, males, obesity, an early bedtime, loud snoring, dyspnea, and night-time open-mouth breathing were all considered possible independent risk factors for NE.²⁸ Moreover, A multitude of studies had also shown that the prevalence of NE in OSA children was about 33–50%, while 54% of children with NE showed some degree of sleep-disordered breathing, which further indicated a significant bidirectional relationship between OSA and NE.^{29,30} Interestingly, the arousal index of NE children with OSA was higher than those without OSA.³¹ However, the study by Banhara et al found that no significant correlation was observed between OSA symptoms and NE, while the Pierre Robin sequence, a congenital craniofacial malformation, served as a greater risk for NE.³²

Health-related quality of life (HRQoL) is described as an individual's comprehensive perception of disease, life condition, and adaptability. It is composed of multidimensional aspects such as physiological, psychological, emotional, social, and spiritual functions, which can evaluate the patient's subjective feelings about medical conditions.³³ Snoring raises the risk of behavioral and psychological issues, as well as decreased HRQoL, in children with monosymptomatic NE. Besides, HRQoL has been negatively impacted by both NE and OSA, ranging in severity from snoring to OSA.³⁴ It has been demonstrated that children with chronic diseases such as NE and OSA had lower HRQoL, which can seriously affect the physical function, emotional state, social function, responsibilities, and health awareness of children and their families.^{35,36} Children with NE often have tension, an inferiority complex, excessive anxiety, and extreme pain and guilt after bed-wetting.³⁵ Children with OSA are also often suffering from the burden of a series of clinical manifestations such as short stature, withdrawal, and low spirit.³⁶ The HRQoL of OSA children, both with and without NE, was found to be identical, indicating that the primary cause causing the HRQoL impairment was OSA rather than NE.¹⁶ However, some studies have found that children with both NE and OSA have a more pronounced impairment in HRQoL compared to children with either NE or OSA alone, suggesting that comorbid NE and OSA have a negative additive effect on HRQoL.³³

Possible Pathogenesis of NE in Children With OSA

Abnormal Secretion of Humoral Factors

Studies have demonstrated that children with OSA have elevated atrial natriuretic peptide (ANP), decreased antidiuretic hormone (ADH), and more nocturnal urine volume.^{1,37,38} The possible mechanism of NE caused by abnormal humoral factors secretion is as follows (Figure 1A). First, due to the repeated OSA in children with OSA during sleep, the partial pressure of blood oxygen gradually decreases and the partial pressure of carbon dioxide gradually increases, forming a hypoxic environment and hypercapnia, which causes pulmonary arterial hypertension and pulmonary vasoconstriction, increasing the cardiac preload and atrial volume.³⁸ Moreover, the negative pressure in the chest increases when the patients try to improve the hypoxia environment, further aggravating the cardiac preload and increasing the atrial volume.³⁹ However, increased cardiac preload and atrial volume is a pull stimulation on the atrial wall, which can stimulate the release of ANP from atrial myocytes.³⁹ ANP has the function of promoting the kidney to expel sodium and water and inhibiting ADH and the renin-angiotensin-aldosterone system.⁴⁰ Increased secretion of ANP can lead to NE. Usually, the ADH level has a rhythm of decreasing day and increasing at night, which causes increased urine reabsorption and reduced urine production during sleep.⁴¹ However, the nocturnal ADH level was lower in children with OSA, producing large amounts of hypotonic urine, which might be that the developing brain of children and normal hormone secretion was affected and the stable circadian rhythm was changed due to the low oxygen environment.⁴² In

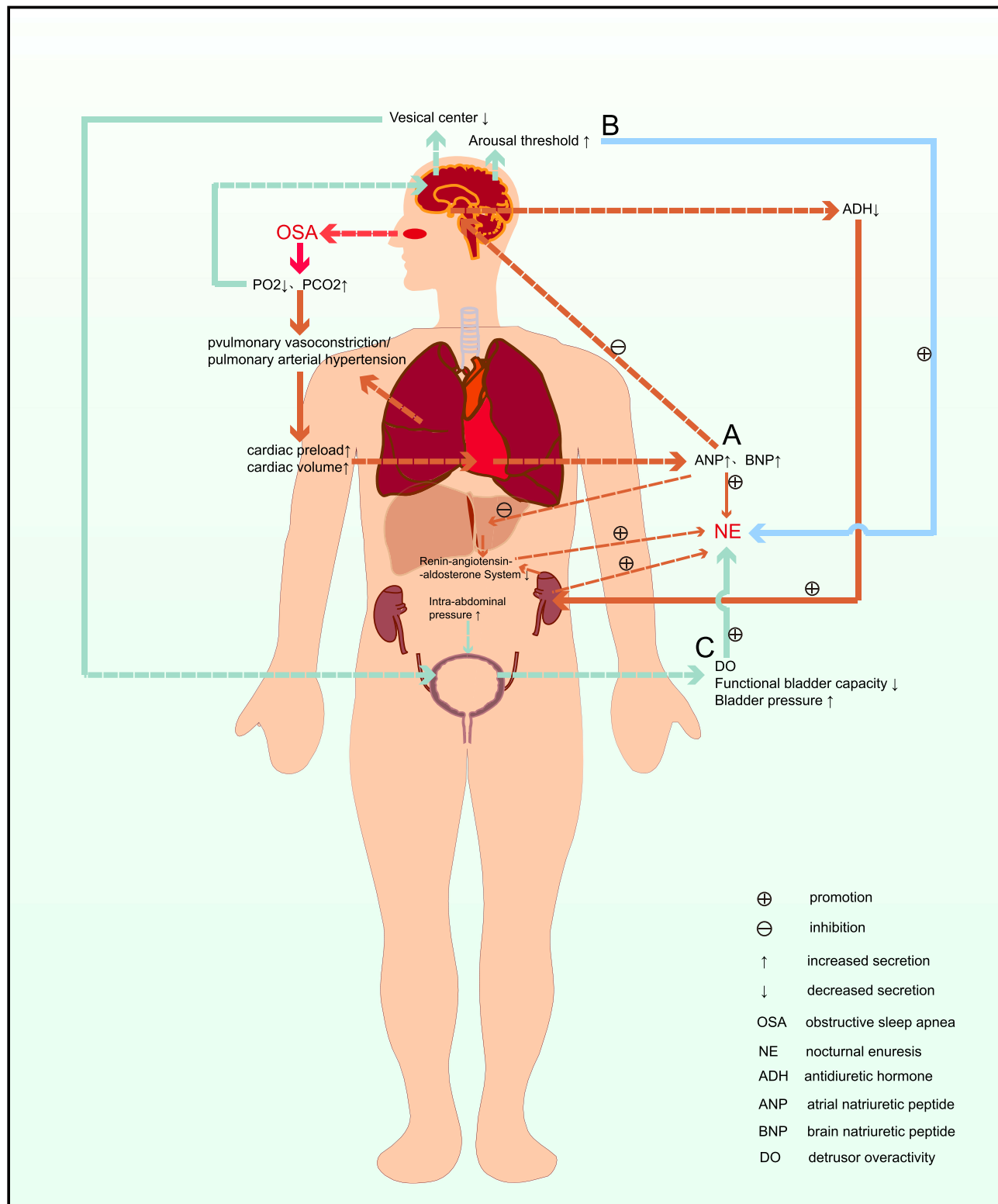


Figure 1 Reflex mechanisms of OSA induced NE. **(A)** Abnormal secretion of humoral factors. **(B)** Sleep-wake disorder. **(C)** Bladder dysfunction.

addition, most children with OSA recovered the normal ANP and ADH levels after adenotonsillectomy (AT), which might be one of the reasons for the improvement of NE symptoms.⁴³

The autonomic nervous system-related neurotransmitters, brain natriuretic peptide (BNP), and endothelin system may also be involved in NE. Studies have shown that decreased sympathetic nerve activity and catecholamines after AT were

also associated with the improvement of NE.⁴⁴ Angeli et al found that children with NE had increased rapid-eye-movement sleep duration, indicating sympathetic overactivity, while patients with overactive bladder had non-rapid-eye-movement sleep-related symptoms of NE, which was possibly related to parasympathetic nerve stimulation. Both sympathetic and parasympathetic overactivities were associated with sleep disorders in children with NE.⁴⁵ Other studies had shown that the BNP was increased in children with OSA and NE, and the degree of increase was related to the severity of OSA.⁴³ BNP is also secreted by cardiomyocytes, which can encourage sodium excretion, prevent the renin-angiotensin-aldosterone pathway, and reduce the release of ADH, thereby promoting urination.⁴⁶ However, a longitudinal prospective intervention study in children aged 5 to 14 years showed that a total of 85.8% of children had partial or complete improvement in NE after airway obstruction surgery and 42.8% showed complete remission with elevated BNP but no increase in the ADH. Thus, the improvement in NE was not explained by synergistic changes in BNP and ADH.⁴¹ Furthermore, the endothelial system was also a potential physiological pathway in NE.⁴⁷ The endothelial pathway has been pointed out to play a critical role in natriuretic, diuretic, and the central regulation of the synthesis of ADH and other hypothalamic hormones, which may indirectly act by affecting ADH and renin-angiotensin-aldosterone system.^{48,49}

Sleep-Wake Disorder

One of the main contributing factors to the pathophysiology of NE in children with OSA is the disruption of the waking mechanism during sleep. The brains of children are not fully developed. Lack of development in the regulation of the hypothalamic sleep-wake centers causes sleep awakening disorder, leading to NE (Figure 1B). Compared to NE children without OSA, the NE children with OSA were more difficult to wake up in the morning by the evaluation of nocturnal polysomnography monitoring, which indicated that the sleep structure of children with OSA was partly related to the occurrence of NE.⁵⁰ NE occurred in children with OSA because they were unable to wake up in time by the regular awakening mechanism, despite the stimulation of bladder filling and detrusor contraction causing a need for micturition.³ Kovacevic et al found that most children could not be awakened before AT but could wake up and urinate after surgery.⁴³ This phenomenon might be because OSA was relieved after AT in children with OSA and normal sleep was not disturbed, allowing normal self-arousal mechanisms to take effect.

Disturbed sleep architecture in children with OSA was manifested by recurrent cortical awakening during sleep.^{9,50} Nocturnal polysomnography showed that children with OSA had frequent cortical awakenings associated with light sleep, but less actual awakenings.⁵⁰ The occurrence of NE was also associated with frequent cortical arousal.⁹ Furthermore, a number of current studies have suggested that deep sleep has been linked to frequent arousal in experimental settings and contributes to NE.^{52–54} Compared to their healthy peers, NE children with OSA were reported to be more likely to experience repeated arousal.⁵¹ Therefore, it was speculated that the mechanism of sleep-wake disorder promoting NE could be summarized. Children with OSA developed a hypoxic environment due to OSA. A hypoxic environment is an arousal stimulus to the brain, which can lead to sleep structure disturbance and repeated cortical arousal, resulting in increased true arousal threshold and decreased sensitivity to bladder filling and detrusor contraction stimulation. The inability to respond to bladder filling or wake up in time led to NE.⁵² Snoring in children with OSA could increase sleep pressure, further raising the awakening threshold.⁵³

Bladder Dysfunction

The detrusor, urethral sphincter, and conscious control work together to produce urination, a complicated positive feedback reflex. Children suffering from OSA may have recurrent periods of intermittent hypoxia, resulting in elevated urinary nerve signaling, detrusor overactivity, internal sphincter contraction, and increased excitability of the bladder receptors, which is one of the reasons for NE (Figure 1C). Studies have found that the pathophysiology of NE was associated with elevated intra-abdominal pressure and bladder pressure resulting from breathing efforts against an obstructed airway.⁵⁴ An important cause of NE in children with OSA was bladder dysfunction, including reduced functional bladder capacity, nocturnal detrusor overactivity, and urethral instability. The detrusor overactivity of NE children will be further aggravated by the deterioration of OSA.²¹ By urodynamics examination, 30% of OSA kids experienced bladder instability according to Watanabe et al.⁵⁵ This might be due to the suppression of the pontine

micturition center caused by the hypoxic environment in OSA children during night sleep, resulting in detrusor over-activity, incomplete bladder relaxation, and decreased bladder volume during urinary storage. A smaller bladder capacity could initiate urination. In addition, the low oxygen environment can also affect the urination reflex arc, causing the bladder to go out of control and leading to NE. However, other studies have shown that children with OSA and NE had longer detrusor contraction time and higher bladder pressure compared to children without NE or OSA, while there were no differences in bladder volume, neuromuscular characteristics, and urethral sphincter function.⁵⁶ This might be due to the need for vigorous breathing in OSA patients, resulting in a significant increase in abdominal and bladder pressure and promoting urination.

Obesity and Psychophysiological Factors

Obesity or overweight is not only a risk factor for OSA but also NE. The association between NE and OSA was more pronounced in children with obesity, and higher AHI was seen among them.^{21,57} On the one hand, this association might be attributed to the fact that obesity could increase upper airway collapse through mechanical effects.⁵⁷ On the other hand, children with obesity have poor mental health and social function, dissatisfaction with their weight, and impaired self-esteem, producing depression, which would cause children with obesity to stay up late, and then affect the release of ADH and promote NE. NE would further increase the psychological burden on children, forming a vicious circle of NE, psychology, and obesity.^{33,57} Moreover, Demirbas et al found that screen time exposure might be a contributing factor to sleep disorder in children with NE, and controlling screen time in childhood within the normal range was thought to contribute to the treatment of NE.⁵⁸ This approach was beneficial and easy to apply, with a positive impact on response to treatment and relapse. However, as required by evidence-based medicine regulations, further randomized controlled studies and meta-analyses were needed to support these results.

In addition, other studies have shown that one possible link between OSA and NE could be inflammation and that obesity played an important role in the inflammatory response.³ More fat cells are found in visceral fat than in subcutaneous fat, which encourages macrophages to secrete more proinflammatory cytokines and triggers an inflammatory response.⁵⁹ There was a strong positive correlation between proinflammatory cytokines level and body mass index in adults, particularly in the region of visceral obesity.⁵⁹ Likewise, it was reported that the inflammatory response was assessed using C-reactive protein levels and the positive correlation between C-reactive protein levels and visceral fat regions in adolescents showed that visceral obesity is the important cause of the systemic inflammatory response.⁶⁰ It has been demonstrated that the severity of OSA was correlated with visceral adiposity in adolescents.⁶¹ According to the aforementioned findings, inflammatory cytokines might be involved in the mediation of OSA and NE in children with obesity. Besides, allergy reactions triggered by inflammatory cytokines in allergic illnesses might result in NE. Studies have found that OSA children with allergy had a much higher chance of developing NE ($P < 0.001$), indicating that there might be a combination of both conditions in the pathophysiology of NE.⁶² While we can hypothesize that inflammatory cytokines may be involved in this relationship, more research is needed to determine the precise mechanism.

Genetics, Gender, and Others

It had been reported that OSA patients had familial clustering, and genetic factors might be related to the pathogenesis of OSA, or it might be that the risk factors associated with OSA were related to heredity. So far, no genetic diagnostic marker genes for OSA have been confirmed.⁶³ Genetic factors played a decisive role in many NE patients. Pedigree analysis and the twin method all showed that NE had a high heritability. It was generally believed that NE followed the pattern of autosomal dominant inheritance. Whether NE and OSA share common genes remains to be further investigated. Nevertheless, behavior and maturational delay remain the most significant cause of NE.⁶⁴

The study found that the severity of OSA was positively correlated with the prevalence of NE. However, OSA girls were more likely to eventually cease NE than boys. Some scholars speculated that it might be due to the different sensitivity of the kidney to different sex hormones.^{37,65}

The state of renal hyperfiltration at night might also be one of the causes of NE. It has been demonstrated that the diastolic blood pressure and excretion of urinary sodium increase in tandem with the severity of OSA. Pressure-induced natriuresis is caused by recurrent increases in systemic blood pressure following nocturnal obstructive episodes.⁶⁶

Effective OSA treatment can control natriuresis and polyuria.⁶⁷ Glomerular filtration fraction was significantly increased in OSA patients, and the extent of its increase was related to the degree of hypoxia. The more severe night-time hypoxia, the more likely patients were to show a renal hyperfiltration state, which further increased nocturnal urine volume. It might be related to the damage of the hypoxia environment to renal tissue structure, resulting in decreased concentration or dilution functions of the kidney.^{68,69}

Improvement of NE by OSA Treatment

Surgical Intervention

For children with OSA, AT is a simple and effective method that may alleviate NE in this population. It is possible that the occurrence of night apnea is reduced by removing the tonsils and adenoids, which reduces the release of ANP and ADH and leads to a normal arousal threshold in turn, thereby effectively alleviating NE.^{71–73} In 1977, Simmons et al first reported two cases of NE in OSA children, but NE was cured after the elimination of OSA by surgery (adenoidal tonsillectomy, tracheotomy).⁷⁰ Interestingly, a child suffering from primary NE with chronic recurrent otitis media with effusion, adenoid hypertrophy, and severe snoring still wet the bed after various treatments, including limiting fluid intake before bedtime and waking the child to urinate at night. However, the phenomenon disappeared immediately without any discomfort after AT.⁵⁶ At present, the cure rate of children with NE and OSA after nasopharyngeal surgery is 62–90%.²³ Similarly, Kaya et al found that 52% of the children with NE had complete resolution for NE. Also, the rest of these children had a significant decrease in NE, and daytime bedwetting occurrence decreased significantly after AT.⁷¹ Ahmadi et al came to a similar conclusion that 51 (60.7%) of the children had fully recovered from NE, and 22 (26.2%) had exhibited some improvement following AT.⁷² Some researchers constructed that NE was resolved in more than half of the OSA children after AT.^{43,74–76}

Nevertheless, considering that spontaneous regression typified the natural history of NE, Snow et al investigated whether AT had additional benefits for children with non-severe OSA.³⁷ According to whether to perform AT, 393 children with non-severe OSA were divided into the observation group (201 patients) and the AT group (192 patients). The results showed that the regression rate of NE was around two times higher comparing the AT group to the observation group. AT had a good clinical efficacy, which suggested that children with non-severe OSA could consider using AT to treat chronic and cumbersome NE problems, especially when parents consulted about the benefits and risks of surgical intervention in children with NE and non-severe OSA. Martenstyn et al reported that the OSA children who received AT were less likely to develop NE compared with those without AT.⁵⁰ The children with NE and severe OSA monitored by nocturnal polysomnosis were more likely to have an improvement in bedwetting after the surgery. This phenomenon may be attributed to the relatively mild OSA as a co-morbid disease of NE, while severe OSA is the pathogenic cause of NE. This speculation needs to be further investigated. Although it had been noted that NE improved following AT,⁶² a different study discovered that not all children with OSA and NE had dryness.⁷⁶ Kalorin et al pointed out that urine incontinence neither before nor after tonsillectomy was correlated with tonsillar hypertrophy.⁷⁷ Similarly, Facundo et al also found that surgical management of airway obstruction had no influence on the resolution of NE for individuals with OSA.⁷⁸ They found no statistically significant differences in age, race, gender, body mass index, NE types, or AHI between patients treated with AT and those who abandoned the treatment. Many studies have shown that children's age, obesity index, comorbidities such as allergic rhinitis and structural airway abnormalities may all affect the outcome of surgical treatment of OSA the improvement of NE.^{77–80} In addition, the criteria for describing OSA was unclear in some prospective studies evaluating the relationship between OSA and primary monosymptomatic NE, which might influence the results.^{80,81} The role of OSA treatment in the improvement of NE children has been mentioned above. Herein, we dissect relevant representative outcomes in the current data (Table 1).

Non-Surgical Treatment

In addition to surgical intervention, some non-surgical treatments, such as positive airway pressure (PAP) therapy, have been found to be effective in improving NE symptoms in patients with OSA. PAP can improve sleep quality, reduce nocturnal awakenings, and enhance oxygenation levels through sustained airway positive pressure, which may indirectly contribute to the alleviation of NE.⁸² Although there are fewer relevant researches, some studies have shown that the

Table 1 Outcome of the Treatment for Obstructive Sleep Apnea in Children With Enuresis Nocturna

Reference	Study Design	Sample Characteristics	Surgery	Outcome
Snow et al, JAMA Otolaryngol Head Neck Surg, 2021 ³⁰	Multicenter randomized clinical trial	453 children with nonsevere OSA and NE, aged 5.0 to 9.9 years	AT	There was a decrease (−11.0%) in the number of children with NE (n = 38)
Martenstyn et al, J Paediatr Child Health, 2021 ⁴¹	Retrospective case-control study	21 children with enuresis and moderate OSA, aged 5–14 years	T&A or AT	Children who had undergone surgery were less likely to have NE than those who had not undergone surgery
Davaro et al, J Pediatr Urol, 2021 ⁶⁶	Population-based study	59 patients with PNE (mean age at diagnosis 8.8 years old)	T&A or CPAP and T&A	Surgical treatment of airway obstruction had no effect on resolution of PNE.
Kaya et al, Int J Pediatr Otorhinolaryngol, 2018 ⁶⁰	Prospective study	19 patients with OSA and NE	AT	52% of the patients with NE had complete resolution of NE and others had a significant decrease in NE
Park et al, Laryngoscope, 2016 ⁶³	Prospective study	17 children with SDB and NE (mean age 8.17 ± 2.84 years)	AT	13 of the 17 NE patients (76.5%) showed complete resolution
Kovacevic et al, J Urol, 2014 ³³	Prospective study	46 children with SDB and NE, aged 5 to 18 years old	AT	43.5% of patients became dry
Ahmadi et al, Iran J Otorhinolaryngol, 2013 ⁶¹	Prospective cohort study	97 children with enuresis, aged 3 to 12 years	AT	NE had resolved completely in 51 (60.7%) children and had shown relative improvement in 22 (26.2%) children.
Kovacevic et al, J Pediatr Urol, 2013 ⁶²	Observational study	101 children with OSA and NE, aged 5–18 years	T&A	49 children responded to T&A (49%), 30 resolved within 1 month postoperatively.
Jeyakumar et al, Laryngoscope, 2012 ²²	Systematic review	587 children with SDB and NE, aged 18 months to 19 years	T&A	Preoperative prevalence of enuresis was 31% (426/1360). The postoperative prevalence of enuresis was 16% (95/587)
Waleed et al, Swiss Med Wkly, 2011 ⁶⁴	Population-based study	47 children with NE with SDB, aged 5–10 years	AT	The improvement was observed in 29 children (87.8%).
Kalorin et al, J Urol, 2010 ⁶⁵	Prospective study	326 children aged 3 to 15 years	T	The respective cure rates for bedwetting were 40% and 50%.
Andreu-Codina et al, Children (Basel), 2024 ⁷⁵	Prospective study	298 children aged 2 to 12 years old	AT	After AT, 49% of the children with OSA and NE significantly improved.

Abbreviations: NE, Nocturnal enuresis; OSA, Obstructive sleep apnea; AT, adenotonsillectomy; T&A, tonsillectomy and adenoidectomy; CPAP, continuous positive airway pressure; T, tonsillectomy.

frequency of nocturnal urination, the nocturnal urine volume, and the nocturia excretion of Na(+) in patients with OSA were significantly reduced after treatment with transnasal continuous PAP.^{84–87} Furthermore, a meta-analysis suggests that continuous PAP may be an effective treatment for reducing NE associated with OSA and improving the quality of life for such patients.⁸⁷ However, researches on the effects of PAP on NE in children are still limited and further exploration and evaluation is urgently needed. Research advances in this field will help deepen our understanding of NE treatment and provide more comprehensive therapeutic strategies.

Strengths and Limitations

We retrospectively summarize the research literature on children NE combined with OSA over the past four decades, and systematically analyze the bidirectional relationship between NE and OSA, the possible mechanisms by which OSA promotes NE, and the effects of surgical and non-surgical interventions of OSA on NE symptoms. This broadens our

understanding of the etiology of NE in children with comorbid OSA and provides new treatment ideas and intervention strategies for the clinicians. In addition, this study also emphasized the complex interaction between children NE and OSA, suggesting that future studies should focus on the in-depth exploration of the relationship between the two, as well as more effective treatments, especially in terms of behavioral interventions and non-surgical treatments for further evaluation. However, there are several restrictions on this review. First of all, this review exclusively covered English literature, and the significant works in other languages were left out of the analysis. Next, this study only used the PubMed database as a data source. Relying on a single data source may result in a less comprehensive understanding of a particular domain, limiting the depth and breadth of the analysis. Therefore, future research could consider integrating other databases and data types to provide a more comprehensive analysis and to remedy the shortcomings of the current study.

Conclusions

The co-incidence of NE and OSA seriously affects the physical and mental health of children. The possible mechanisms of NE in children with OSA are that abnormal humoral factors (including ANP, ADH, BNP, catecholamines, renin-angiotensin-aldosterone system, inflammatory factors, etc) and dysfunction of kidney self-regulation lead to more nighttime urine volume in children. Abnormal regulation of the central nervous system and urination reflex promote overactivity of the bladder and aggravate instability of the bladder at night. The elevated arousal threshold due to sleep-wake disorder makes children with OSA unable to wake up without responding to bladder-filling signals or detrusor contraction stimulation. Obesity, psycho-psychological factors, genetics, gender, and family factors further promote the formation of NE, which ultimately leads to bedwetting in children with OSA. The exact mechanism of NE is not yet conclusive, but ANP levels and sleep-wake disorders may play a crucial role, and AT and PAP can benefit children with OSA and NE co-morbidity. In conclusion, a comprehensive multidisciplinary evaluation of children with NE and OSA is needed, and further studies are needed on the pathogenesis, prevention, and treatment of NE in children with OSA.

Abbreviations

NE, Nocturnal enuresis; OSA, Obstructive sleep apnea; AT, Adenotonsillectomy; ANP, Atrial natriuretic peptide; ICCS, International Children's Continence Society; AHI, Apnoea-hypopnoea index; HRQoL, Health-related quality of life; ADH, Antidiuretic hormone; BNP, Brain natriuretic peptide; PAP, Positive airway pressure.

Consent for Publication

All authors have seen and approved the manuscript and consent publication.

Author Contributions

All authors made a significant contribution to this work, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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