



## Do Sleep Disorders Influence the Prognosis and the Response to the Therapy in Enuretic Children?

### ABSTRACT

**Objective:** The current study describes the prevalence of sleep disorders in enuretic children, playing as influencing factors in the response to treatment and risk of relapse.

**Materials and methods:** Data were collected from September 2020 to February 2021 in 114 children aged between 5 and 14 years, with a diagnosis of nocturnal enuresis and concomitant sleep disorders, referred to the Pediatric Unit, Campus Bio-Medico University, Rome. Enuretic children were subjected to an anamnestic and clinical assessment. Sleep disorders investigated were sleep apnea, sleep talking, snoring, bruxism, restless sleep, and somnambulism. Each patient was subjected both to pharmacological and to non-pharmacological treatments and monitored for 3 months to identify the presence of relapse. Patients were divided into 2 groups according to therapy response, and statistical analysis was performed to evaluate possible variables involved in enuresis relapse.

**Results:** A high prevalence of sleep disorders was documented: 8/114 children (7%) had sleep apnea, 47/114 (41.2%) had bruxism, 66/114 (57.8%) had snoring, 54/114 (47.3%) had sleep talking, 18/114 (15.7%) had restless sleep. Forty-three of 114 children (37.7%) had relapses: 21/43 (49%) relapses occurred in children with only 1 sleep disorder, while 22/43 (51%) relapses occurred in children with 2 or more sleep disorders. Lower risk of relapses was reported in children subjected to dual therapy.

**Conclusion:** Sleep disorders were widely associated with nocturnal enuresis, acting as comorbidities in the clinical course of nocturnal enuresis. Combined therapy seems to be associated with a lower rate of relapse of enuresis in a 3-month follow-up. A multi-disciplinary approach is required to improve patients' management.

**Keywords:** Enuresis, sleep-wake disorders, bruxism, recurrence

### Introduction

Sleep disorders are one of the main problems in childhood, with a prevalence at least of 25%-50% and a peak onset between 3 and 8 years.<sup>1-3</sup> According to the International Classification of Sleep Disorders, sleep problems are grouped into 6 categories: insomnia, sleep-related breathing disorders (SDB), central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, and parasomnias.<sup>4</sup> Sleep disorders have a significant impact on physiological, physical, and behavioral development, affecting multiple aspects of a child's life. Pediatricians have to identify sleep problems to prevent a wide range of negative outcomes, such as fatigue and lethargy, headaches, behavioral problems and mood disturbance, cognitive impairment, and poor school results.<sup>1-3</sup> Sleep disorders could have a pathological role as comorbidities or predisposing factors in the onset and progression of nocturnal enuresis (NE), a common problem in children, defined as wetting that occurs during sleeping more than 3 times per week after 5 years of age.<sup>5,6</sup> According to the International Children's Continence Society (ICCS), NE is defined as monosymptomatic nocturnal enuresis (MNE) if it occurs without any other lower urinary tract symptoms and a history of bladder dysfunction and non-monosymptomatic nocturnal enuresis (NMNE) if it is characterized by concomitant daytime incontinence.<sup>7</sup> Primary enuresis is defined in a child

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that was never “dry” for longer than 6 consecutive months, whereas the term secondary enuresis is used for new-onset enuresis after a dry period at least of 6 months.<sup>8</sup> Several studies have investigated the relationship between sleep quality and NE.<sup>6,9,10</sup> Children with NE are usually called “deep sleepers” because of a high arousal threshold, one of the pathogenetic factors underlying NE, even if the sleep architecture is normal as documented by polysomnography. By contrast, anomalies in the electroencephalography patterns have been described during sleep in enuretic patients.<sup>11</sup> Enuretic children are usually confused and drowsy when awoken from sleep at night, supporting the hypothesis that NE is connected to a disorder of arousal.<sup>12</sup> An increased incidence of sleep disorders, such as parasomnias, occurs in enuretic children. Moreover, NE could improve after adequate treatment of sleep disorders: for example, the association between enuresis and SDB in children is supported by a documented improvement or a resolution of enuresis after successful treatment of SDB.<sup>7,12</sup>

The primary aim of our study was to investigate the role of sleep disorders in NE, focusing on therapy response and the risk of relapse. Secondly, we investigated the prevalence of sleep disorders, alone or together, in enuretic children to demonstrate the high presence of such comorbidity.

## Materials and Methods

### Population

A cross-sectional cohort of children and adolescents with enuresis was identified. We enrolled 150 patients, of which 106 were males and 44 were females, aged between 5 and 14 years from September 2020 to February 2021. We included children with NE according to the ICCS definition, while the only exclusion criterion was the absence of sleep disorders. Diagnosis of NE was based on anamnestic and clinical evaluation, including the investigation of risk factors (such as family history, sleep disorders, arousal difficulties, and psychological triggers), and on a bladder diary to record incontinence episodes, nighttime urinary volume, daytime frequency, and volume.<sup>8</sup> We diagnosed sleep disorders based on parental administered sleep questionnaires about typical symptoms and signs, such as mouth breathing and hyponasal speech, obtaining a detailed history from them. We also investigated the global quality of sleep with questions about family history, time taken to sleep onset, total duration of nocturnal sleep, the quality of morning awakenings, and the daytime difficulty to stay awake.

We have chosen pharmacological treatment with desmopressin or oxybutynin or a combination of both. Despite the effectiveness of the alarm treatment, we did not use it in our study because of the poor compliance of patients and their families.<sup>13,14</sup>

### MAIN POINTS

- *Our study provides a detailed description of the most common sleep disorders in children suffering from enuresis.*
- *We found that sleep disorders were not associated with enuresis relapse in children.*
- *Our study showed that combined therapy with desmopressin and oxybutynin can significantly reduce the risk of relapse in children with enuresis.*

Furthermore, sleep disorders and therapy were analyzed in 2 subgroups of subjects with (n = 71) and without (n = 43) enuresis relapse after therapy.

### Data Collection

Data collected about NE included gender, type of symptoms (nocturnal or diurnal), type of therapy, age, and the presence of relapse. Sleep disorders were investigated by taking a sleep history and conducting a careful medical assessment. We focused on the main sleep disorders in NE: sleep apnea, bruxism, sleep talking, snoring, somnambulism, and restless sleep.<sup>15</sup> The suspicion of obstructive sleep apnea syndrome was based on anamnestic and clinical criteria. More specifically, the anamnestic information we investigated was the presence of habitual snoring (3 or more nights a week), presence of breathing difficulties during sleep (apneas, noisy breathing, or gasping), preferred position during sleep (sitting or with hyperextended neck), cyanosis, headache on awakening, daytime sleepiness, and cognitive and behavioral deficits.<sup>16</sup> The questions used to diagnose other sleep disorders are summarized in Supplementary Table 1.

According to the ICS recommendations, we provided some advice to parents, such as dietary recommendations (avoiding dairy products and a protein-rich diet), fluid restriction in the evening, regular bladder emptying before going to sleep, physical exercises to improve pelvic floor strength, and bladder control. In addition, drug therapy was prescribed: desmopressin if children showed only nocturnal symptoms, oxybutynin if children showed diurnal symptoms, and desmopressin in association with oxybutynin if children suffered from both.

### Follow-Up

Each patient was treated and monitored for 3 months. During the follow-up time, NE and the response to treatment were evaluated with a NE calendar and a bladder diary to collect information about the frequency of urination, urinary leakage, and signs of urgency. According to ICCS, relapse was defined as more than 1 episode of bed wetting per week.

### Statistical Analyses

Categorical variables were reported as count and percentage and were analyzed using a  $\chi^2$  test, while continuous variables were expressed in terms of mean and SD. A Mann–Whitney *U*-test was used to compare nonparametric variables between subjects with and without therapy relapse. A chi-square test was used to compare the differences in terms of the presence of sleep disorders and treatment between the 2 groups of patients. Statistical significance was established at an alpha of 0.05. Analysis was performed using IBM’s Statistical Package for Social Sciences software 25.0 (IBM SPSS Corp.; Armonk, NY, USA) and GraphPad Prism software 9.0.0 (San Diego, Calif, USA).

This study was conducted following the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996) and was approved by the Local Ethical Committee with no protocol number. The study was written in accordance with Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. Children and their families were asked to participate in the study at the end of the clinical evaluation and after 3 months of observation. All patients signed written informed consent.

## Results

We evaluated 150 children, of which 36 were excluded. One hundred fourteen children were eligible for the study, of which 82 were males (72%) and 32 were females (28%): in particular, 49 (43%) were MNE, while 65 (57%) were NMNE. Eighty-six children had primary enuresis, while 28 had secondary enuresis. The sample was subjected to therapeutic measures: 50/114 patients (44%) were treated with desmopressin, 13/114 (11%) with oxybutynin, 41/114 (36%) with desmopressin and oxybutynin. Ten out of 114 patients were not subjected to any drug, and nocturnal/diurnal symptoms were treated conservatively, with bladder training and parental education. The mean age of starting the therapy was  $7.89 \pm 2.36$  years. Descriptive characteristics are shown in Table 1.

Children were affected by the following sleep disorders: 8/114 children (7%) had sleep apnea, 47/114 (41.2%) had bruxism, 66/114 (57.8%) had snoring, 54/114 (47.3%) had sleep talking, and 18/114 (15.7%) had restless sleep. Coexistence of 2 or more sleep disorders was frequent in our cohort: sleep apnea and snoring were found in 4/114 children (3.5%), of which 2 had sleep talking too; sleep talking was exclusively found with sleep apnea in 1 child. Eight out of 114 children (7%) had bruxism and sleep talking, 5/114 (4.3%) had bruxism and snoring; 7/114 (6.1%) had bruxism, snoring, and restless sleep; 1 child had bruxism, sleep apnea, sleep talking, and snoring; and 1 child had bruxism, sleep apnea, snoring, and restless sleep. Snoring and restless sleep were found in 4/114 children (3.5%). Restless sleep is associated in 1 child with sleep talking, in another 1 with bruxism, and in 6/114 children (5.2%) with both disorders.

During the follow-up, relapse occurred in 43/114 children (37.7%), of which 31 were males and 12 were females. No association was found between therapy relapse and age ( $P=.28$ ), sex ( $P > .99$ ), and diurnal symptoms ( $P=.56$ ). In particular, we investigated the association between sleep disorders and the frequency of relapse: there was 51% bruxism, 51% sleep talking, 7% sleep apneas, 44% snoring, and 20% restless sleep in children who developed relapse. Data showed a lower frequency of treatment relapse in enuretic children with snoring ( $P=.01$ ), while no significant association was found in children affected by other sleep disorders, in particular sleep apnea ( $P=.97$ ), somnambulism ( $P > .99$ ), bruxism ( $P=.10$ ), nocturnal speaking ( $P=.57$ ), and agitation ( $P=.17$ ). Data are shown in Table 2. Furthermore, therapy relapse was studied in children who received combined therapy (desmopressin and oxybutynin) versus monotherapy (either desmopressin or oxybutynin). Our analyses showed a lower rate of relapse in patients treated with combined therapy ( $P=.01$ ).

**Table 1.** Descriptive Characteristics and Sleep Disorders in Enuretic Children

Age (years)	7.89 ± 2.36
Gender (male/female)	82/32
MNE/NMNE	49/65
Sleep apnea	8 (7%)
Bruxism	47 (41.2%)
Snoring	66 (57.8%)
Sleep talking	54 (47.3%)
Restless sleep	18 (15.7%)

MNE, monosymptomatic nocturnal enuresis; NMNE, non-monosymptomatic nocturnal enuresis.

**Table 2.** Frequency of Sleep Disorders in Patients With and Without Response to Therapy

Demographics	Responders	Relapsers	P
	(n = 71)	(n = 43)	
Age (years)	7.8 ± 2.4	8.1 ± 2.2	.28
Gender (male/female)	51/20	31/12	>.99
Sleep disorders			
Sleep apnea	5 (7%)	3 (7%)	.97
Bruxism	25 (35%)	22 (51%)	.10
Snoring	47 (66%)	19 (44%)	.01*
Somnambulism	0	0	>.99
Sleep talking	32 (45%)	22 (51%)	.57
Sleep agitation	9 (13%)	9 (20%)	.17

Mann-Whitney U-test and chi-square test were performed; P-value < .05 was set as statistically significant.

\*Statistically significant; P-values are expressed in italic.

## Discussion

Sleep disorders and NE are common pediatric issues, affecting a wide number of children, with consequences both in physical and in psychological development. A double relationship could explain the concomitant presence of these disorders. Nocturnal polyuria, detrusor overactivity, and a failure to awaken in response to bladder sensations may constitute potential pathogenetic mechanisms to explain NE.<sup>17</sup> The cause of NE may be related to difficulty in waking up because of deeper sleep and fragmentation of sleep in enuretic children.<sup>9,18,19</sup> This difficulty could be related to poor sleep quality, due to the fear or the anxiety of bed-wetting during sleep, which children often perceive as a fault. Several studies have been conducted to investigate, in enuretic children, the prevalence of sleep disorders, which predispose them to suffer from sleep deprivation, leading to an elevated arousal threshold or a reduced secretion of vasopressin during sleep, which would be the underlying pathophysiology of NE. Moreover, it seems that NE and some sleep problems may share the same dysfunctional neural circuits, resulting in an increased rate of comorbidity.<sup>20</sup> Most studies have focused on the relationship between NE and sleep disorders, showing an increased incidence of sleep disorders in enuretic or previously enuretic children. Children with NE are 1.5 times more likely to have such sleep problems as compared to those without NE. Ferrara et al<sup>21</sup> in a 2019 study based on a national population database documented a high prevalence of sleep disorders in enuretic children: snoring (13.7%), restless sleep (5.7%), somniloquy (23.7%), and bruxism (14.7%). Our study reflected the observation of the scientific literature, documenting a high prevalence of sleep disorders in enuretic children: 8/114 children (7%) had sleep apnea, 47/114 (41.2%) had bruxism, 66/114 (57.8%) had snoring, 54/114 (47.3%) had sleep talking, and 18/114 (15.7%) had restless sleep. Despite not being statistically significant, 49% of relapses occurred in patients affected by 1 sleep disorder, while 51% occurred in children with 2 or more sleep disorders. Our study showed a high prevalence of sleep disorders in enuretic children; however, no statistically significant association was found between sleep disorders and enuresis relapse, with the exception of snoring which was associated with a lower relapse risk. This may be related to the fact that some patients underwent adenotonsillectomy. Further studies with larger cohorts may allow to better interpret and confirm our findings; of interest, it would be noteworthy to study therapy relapse in patients affected

with snoring and undergoing adenotonsillectomy. Furthermore, our study showed an association between the incidence of relapses and the type of therapy; indeed, children subjected to desmopressin and oxybutynin had a reduced risk of relapse compared to children receiving monotherapy.

### Limitations

We acknowledge that our study has some limitations. The main limitation of the study is the limited number of patients investigated; these findings need to be confirmed in a larger sample of patients, using more reliable tools for sleep apnea diagnosis (polysomnography and standardized tests) and focusing on influencing factors such as patient features (such as BMI, comorbidity, medications used, and family history) and considering still unknown pharmacological mechanisms. Although data showed a lower incidence of enuresis relapse in children treated with combined therapy, we are not able to explain whether this association underlies a causal relationship. Therefore, larger longitudinal and interventional studies are warranted to shed light on the association linking sleep disorders, combined therapy, and enuresis relapse in children. The future perspectives of our study are to evaluate psychiatric symptoms in enuretic children. Furthermore, the inclusion of a control group of children without sleep disorders could allow us to compare the risk of relapse and the potential role of sleep disorders as predisposing factors in the response to therapy.

In conclusion, our findings remarked an association between sleep disorders and NE, acting as comorbidities and influencing each other. Pediatricians should investigate all the aspects of children's living with NE and promote a multidisciplinary approach, including a sleep hygiene and psychosocial support.

**Ethics Committee Approval:** Ethical committee approval was received from Pediatric Unit of Campus Bio-medico University Hospital (Date: September 2020).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Supplementary Table 1.** Questions asked to caregivers in order to diagnose bruxism, sleep talking, snoring, and restless sleep

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Bruxism	Does the child ever grind his teeth during sleeping?
Sleep talking	Does the child ever talk or mumble during sleeping?
Snoring	Does the child ever snore during sleeping?
Somnambulism	Does the child ever get up during sleeping, performing actions such as walking?
Restless sleep	Is the child restless during sleeping?

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