

# Primary nocturnal enuresis as a risk factor for sleep disorders: an observational questionnaire-based multicenter study

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**Introduction:** Primary nocturnal enuresis (PNE) is a common problem in developmental age with an estimated overall prevalence ranging from 1.6% to 15%, and possible persistence during adolescence. There is a growing interest in the sleep habits of children affected by PNE, which is derived from the contradictory data present in clinical literature. The aim of the present study was to evaluate the presence of sleep disturbances in a population of children affected by PNE, and to identify whether PNE could be considered as a risk factor for sleep disturbances among children.

**Materials and methods:** A total of 190 PNE children (97 males, 93 females) aged 7–15 years, (mean  $9.64 \pm 1.35$  years), and 766 typically developing children matched for age ( $P = 0.131$ ) and gender ( $P = 0.963$ ) were enrolled. To evaluate the presence of sleep habits and disturbances, all of the subjects' mothers filled out the Sleep Disturbances Scale for Children (SDSC), a questionnaire consisting of six subscales: Disorders in Initiating and Maintaining Sleep (DIMS), Sleep Breathing Disorders (SBD), Disorders of Arousal (DA), Sleep–Wake Transition Disorders (SWTD), Disorders of Excessive Somnolence (DOES), and Nocturnal Hyperhidrosis (SHY). The results were divided into "pathological" and "normal" scores using a cut-off value (pathological score = at least three episodes per week), according to the validation criteria of the test. Then, the Chi-square test was used to calculate the statistical difference and a univariate logistic regression analysis was applied to determine the role of PNE as a risk factor for the development of each category of sleep disorders and to calculate the odds ratio (OR).

**Results:** PNE children show a higher prevalence of all sleep disturbances (41.03% DIMS; 85.12% SBD; 63.29% DA; 67.53% SWTD; 31.28% DOES; 37.92% SHY; 25.33% SDSC total score), and according to OR results (SDSC total score OR = 8.293, 95% confidence interval [CI] = 5.079–13.540; DIMS OR = 7.639, 95% CI = 5.192–11.238; SBD OR = 35.633, 95% CI = 22.717–55.893; DA OR = 13.734, 95% CI = 9.476–19.906; SWTD OR = 14.238, 95% CI = 9.829–20.625; DOES OR = 5.602, 95% CI = 3.721–8.432; SHY OR = 6.808, 95% CI = 4.608–10.059), PNE could be considered as a risk factor for the development of sleep disorders.

**Conclusion:** Among PNE children, sleep could be strongly altered, thus helping to affirm the hypothesis that PNE tends to alter sleep architecture, or it could itself be the consequence of an abnormal sleep structure. The findings also point to the existence of a potential increase in the risk of developing sleep disorders in the presence of PNE.

**Keywords:** primary nocturnal enuresis, SDSC, sleep

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## Introduction

According to the International Children's Continence Society criteria,<sup>1</sup> nocturnal enuresis is defined as the involuntary loss of urine during the night in children over 5 years

of age, distinguished in a primary form (primary nocturnal enuresis [PNE]), and in a secondary form (secondary nocturnal enuresis).<sup>2</sup> Moreover, nocturnal enuresis is divided into monosymptomatic nocturnal enuresis with no daytime urinary symptoms and nonmonosymptomatic nocturnal enuresis, if accompanied by daytime urinary symptoms.<sup>1</sup>

In general, nocturnal enuresis is a common problem during development, with an estimated overall prevalence ranging from 1.6% to 15%,<sup>3–5</sup> and possible persistence during adolescence.<sup>6</sup> Bedwetting could be considered more common in boys, whereas daytime incontinence is prevalent in girls.<sup>7</sup> The prevalence of nocturnal enuresis tends to decrease with age, supporting the traditional idea of maturational delay in voiding control, even if other mechanisms may be involved.

For years, PNE was interpreted as only resulting from unspecified psychological troubles, with no consideration for an interesting recent suggestion that PNE shares similarities with another very common symptom that occurs in developmental age – migraine without aura.<sup>8</sup> In fact, enuresis and migraines could be linked by cortical system arousal dysfunction, vegetative hyperactivity,<sup>9–11</sup> alteration in motor and visual coordination,<sup>12–14</sup> and sleep disorders.<sup>15–17</sup> As such, PNE and migraines could be interpreted as forms of familial stressors.<sup>18,19</sup>

From this perspective, PNE could be identified as a sort of “periodic syndrome,”<sup>20</sup> such as growing pains, motion sickness, and others that share many of the same aspects as migraine, also considered their effects on learning abilities.<sup>21,22</sup> In this light, the treatment should not exclude the causal role of both sleep disorders and abnormal behavior,<sup>23</sup> while considering natural approaches such as sleep hygiene,<sup>24</sup> nutraceuticals,<sup>25,26</sup> and weight loss.<sup>27</sup>

On the other hand, there is a growing interest in the sleep habits of children affected by PNE, which is derived from the contradictory data present in the clinical literature. For example, in 2008, Nevéus<sup>28</sup> pinpointed the common parental report of deep sleep compared to controls, despite the low efficiency found in the quality of nighttime sleep as reported by children. Moreover, polysomnographic studies conducted among individuals affected by PNE are scarce or have been performed on small samples, with no conclusive data.

In 2009, Dhondt et al<sup>29</sup> reported their polysomnographic findings of 29 subjects with refractory enuresis. The authors noted an increase in the periodic limb movement percentage and a sort of intrinsic hypnic instability, with a high threshold in cortical arousability,<sup>29</sup> even if this alteration could be not identified as the unambiguous pathogenic mechanism.

The aim of the present study was to evaluate the presence of sleep disturbances in a population of children affected by PNE and to identify whether PNE could be considered as a risk factor for sleep disturbances among children.

## Materials and methods

The study population consisted of 190 children (97 males, 93 females) aged 7–15 years (mean  $9.64 \pm 1.35$  years), who were consecutively referred from primary care pediatricians for PNE. The patients were referred to the following clinics between November 2011 to December 2012: the Center of Sleep Disorders for Developmental Age of Child and Adolescent Neuropsychiatry Clinic at the Second University of Naples; to the Unit of Child and Adolescent Neuropsychiatry of the Perugia University; to the Azienda Sanitaria Locale of Terni; and to the Department of Psychiatry of the University of Catanzaro.

The study population was compared with a group composed by 766 typically developing children (390 males, 376 females) matched for age ( $P = 0.131$ ) and gender ( $P = 0.963$ ), who were recruited from the Campania, Umbria, and Calabria school regions.

All children affected by defined psychiatric illness (ie, schizophrenia, psychosis, attention deficit hyperactivity disorder), mental retardation (intelligence quotient  $< 75$ ), neurological diseases (ie, epilepsy, neuromuscular disorders, cerebral palsy), symptoms of lower urinary tract malfunction and/or infection, overweight (body mass index [BMI]  $\geq 85$ th percentile), or obesity (BMI  $\geq 95$ th percentile) were excluded.

Data were collected from a pilot group (ten PNE, ten control children) and used to perform the sample size calculation. The desired power was set at 0.80 and error at 0.05. The sample size was calculated using online software ([http://www.dssresearch.com/toolkit/sscalc/size\\_a2.asp](http://www.dssresearch.com/toolkit/sscalc/size_a2.asp)). The sample size required was found to be 13 subjects for each group, but there was the opportunity to recruit more patients (956 in total) in order to strengthen our findings.

## Sleep habits assessment

To evaluate sleep habits and disturbances, all of the subjects' mothers filled out the Sleep Disturbances Scale for Children (SDSC),<sup>30</sup> a standardized questionnaire for the assessment of sleep problems during development, consisting of 26 items grouped into six subscales: Disorders in Initiating and Maintaining Sleep (DIMS), Sleep Breathing Disorders (SBD), Disorders of Arousal (DA), Sleep–Wake Transition Disorders (SWTD), Disorders Of Excessive Somnolence (DOES), and Nocturnal Hyperhidrosis (SHY). Both the

original or modified versions of this measure are widely used in school-aged children.<sup>31–35</sup>

According to the SDSC validation criteria,<sup>30</sup> scores  $\geq 71$  for the SDSC total score,  $\geq 17$  for DIMS,  $\geq 7$  for SBD,  $\geq 6$  for DA,  $\geq 14$  for SWTD,  $\geq 13$  for DOES, and  $\geq 7$  for SHY were considered as pathological.

The subjects in both groups were recruited from the same urban area; participants were Caucasian, and held a middle-class socioeconomic status.

All parents gave their written informed consent. The study was conducted according to the criteria of the Declaration of Helsinki.<sup>36</sup>

## Statistical analysis

Mean differences in anthropometric (BMI z-score) and clinical characteristics between the PNE individuals and the control group were analyzed by *t*-test.

In order to evaluate the differences among both groups (PNE and controls) in terms of the prevalence of the pathological items of the SDSC, the results were divided into “pathological” and “normal” scores using a cut-off value (pathological score = at least three episodes per week), according to the validation criteria of the test. Then, the Chi-square test was used to calculate the statistical difference.

The Bonferroni correction was applied, and *P*-values  $< 0.01$  were considered to be statistically significant. Moreover, an univariate logistic regression analysis was applied to determine the role of PNE as a risk factor for the development of each category of sleep disorders and to calculate the odds ratio (OR). The commercially available Statistica software (StatSoft Inc, Tulsa, OK, USA) was used for the statistical evaluation.

## Results

Two study groups were matched for age ( $P = 0.131$ ), gender ( $P = 0.963$ ) and BMI z-score ( $P = 0.230$ ), as shown in Table 1.

**Table 1** Demographic and anthropometric characteristics of children affected by PNE and controls

	PNE (n = 190)	Normal (n = 766)	P
Age	9.64 ± 1.35	10.02 ± 3.44	0.131
Sex ratio (M/F)	97/93	390/376	0.963
z-BMI	0.63 ± 0.38	0.59 ± 0.42	0.230

**Notes:** In order to verify the gender matching (M/F), the Chi-square test was applied; all other characteristics were evaluated by *t*-test analysis.

**Abbreviations:** PNE, primary nocturnal enuresis; n, number; M, male; F, female; z-BMI, z-score body mass index.

Table 2 shows the higher prevalence of pathological responses among children affected by PNE across 21 items when compared to control subjects, while the remaining four items (reluctance to go to sleep, presence of more than two awakenings per night, difficulty to go back to sleep, sleep apnea) do not differ significantly. Moreover, PNE individuals showed higher scores across the SDSC total ( $P < 0.001$ ), DIMS ( $P < 0.001$ ), SBD ( $P < 0.001$ ), DA ( $P < 0.001$ ), SWTD ( $P < 0.001$ ), DOES ( $P < 0.001$ ), and SHY ( $P < 0.001$ ) scores than controls.

Finally, according to the results of the logistic regression analysis, PNE could be considered as a risk factor for developing sleep disorders according to the following results: SDSC total score (OR = 8.293, 95% confidence interval [CI] = 5.079–13.540); DIMS (OR = 7.639, 95% CI = 5.192–11.238); SBD (OR = 35.633, 95% CI = 22.717–55.893); DA (OR = 13.734, 95% CI = 9.476–19.906); SWTD (OR = 14.238, 95% CI = 9.829–20.625); DOES (OR = 5.602, 95% CI = 3.721–8.432); and SHY (OR = 6.808, 95% CI = 4.608–10.059) (Table 3).

## Discussion

In general, the acquisition of urinary continence seems to be complex and has probably not yet been completely understood.<sup>37</sup> On the other hand, PNE could be considered one of the most common and disabling problems during development, yet it is still regarded as simple bedwetting, in spite of it being identified as a different condition, and presenting with various comorbidities such as neuromotor problems,<sup>38</sup> attention difficulties,<sup>39</sup> learning disabilities, and the possibility of being an epiphenomenon of other symptoms, or the effect of particular psychological states.<sup>40,41</sup>

Paradoxically, sleep disorders might be considered to be the most important comorbidity in enuretic children given the growing amount of evidence suggesting a significant relationship with particular anatomical patterns,<sup>42</sup> obesity,<sup>43,44</sup> breathing disorders during sleep,<sup>45–47</sup> and various comorbidities,<sup>48</sup> even if the relationship with other sleep disturbances has not yet been investigated. In this light, our findings tend to show that there is a higher prevalence of PNE children than typically developing children across all classes of sleep disturbances.

The pathogenesis of enuresis could be considered based on a mutual balance of three basic mechanisms: bladder capacity; nocturnal production of urine; and the threshold of arousability,<sup>49</sup> all of which are elevated in the enuretic subject,<sup>50</sup> as confirmed by the higher prevalence of DA and SWTD in our PNE sample (Table 3).

**Table 2** Different percentages of pathological items on the SDSC scales ( $\geq 3$ /week) within the group of enuretic children who underwent the PSG study, with a starting population of enuretic children and a control group

	PNE (n = 190) (%)	Control (n = 766) (%)	Chi-square values	P <sup>a</sup>
1. Sleep less than 8 hours	58.95	16.32	146.100	<0.001
2. Sleep latency > 30 minutes	33.16	6.53	101.040	<0.001
3. Reluctant to go to bed	34.74	36.95	0.232	NS
4. Difficulty getting to sleep at night	40	16.45	49.265	<0.001
5. Anxiety when falling asleep	61.58	7.7	290.618	<0.001
6. Hypnic jerks	61.05	13.05	197.803	<0.001
7. Rhythmic movements while falling asleep	36.84	8.62	97.100	<0.001
8. Vivid dream-like scenes while falling asleep	35.79	5.09	141.263	<0.001
9. Falling asleep sweating	41.58	10.18	107.057	<0.001
10. More than two awakenings per night	12.10	12.4	0.000	NS
11. Difficulty to fall asleep after awakenings	8.42	12.66	2.237	NS
12. Nocturnal hyperkinesia	26.84	21.41	2.275	NS
13. Sleep breathing difficulties	68.95	12.4	266.527	<0.001
14. Sleep apnea	6.32	6.01	0.000	NS
15. Snoring	54.74	17.23	113.168	<0.001
16. Night sweating	64.74	13.19	222.644	<0.001
17. Sleepwalking	22.11	6.66	39.626	<0.001
18. Sleep talking	51.58	18.15	89.481	<0.001
19. Teeth grinding	34.21	6.79	104.046	<0.001
20. Sleep terrors	25.26	5.09	72.465	<0.001
21. Nightmares	48.95	12.01	130.731	<0.001
22. Difficulty in waking up in the morning	41.05	32.38	4.721	<0.001
23. Awakes in the morning feeling tired	45.26	27.94	20.426	<0.001
24. Sleep paralysis	34.21	7.57	94.003	<0.001
25. Daytime somnolence	27.89	9.4	44.207	<0.001
26. Sleep attacks	15.79	3.13	43.143	<0.001
Total SDSC	16.32	2.35	58.224	<0.001

**Notes:** The total SDSC scale value was considered pathologic if  $\geq 71$ . <sup>a</sup>Bonferroni corrected P-value.  $P < 0.01$  was significant.

**Abbreviations:** SDSC, Sleep Disturbance Scale for Children; PSG, polysomnography; NS, not significant.

**Table 3** The differences in the prevalence of pathological scores on the SDSC test between children affected by PNE and typically developing children (normal)

	PNE (n = 190) (%)	Normal (n = 766) (%)	Chi-square	P	OR	95% CI
DIMS	41.03	8.29	126.121	<0.001	7.639	5.192–11.238
pathological score						
SBD	85.12	13.94	379.169	<0.001	35.633	22.717–55.893
pathological score						
DA	63.29	11.09	241.869	<0.001	13.734	9.476–19.906
pathological score						
SWTD	67.53	12.63	250.131	<0.001	14.238	9.829–20.625
pathological score						
DOES	31.28	7.41	77.407	<0.001	5.602	3.721–8.432
pathological score						
SHY	37.92	8.27	108.078	<0.001	6.808	4.608–10.059
pathological score						
SDSC TOT	25.33	3.98	89.752	<0.001	8.293	5.079–13.540
pathological score						

**Abbreviations:** SDSC, Sleep Disturbance Scale for Children; PNE, primary nocturnal enuresis; n, number; OR, odds ratio; CI, confidence interval; DIMS, Disorders in Initiating and Maintaining Sleep; SBD, Sleep Breathing Disorders; DA, Disorders of Arousal; SWTD, Sleep–Wake Transition Disorders; DOES, Disorders Of Excessive Somnolence; SHY, Nocturnal Hyperhidrosis; NS, not significant.

Bader et al<sup>51</sup> showed that the sleep macrostructure of children affected by bedwetting could be considered as normal, even if characterized by the high presence of autonomic arousals before the voiding episodes, denying in this way the impairment in arousability.<sup>51</sup> However, more recently, another sleep study was conducted on 35 enuretic subjects who were compared to 21 healthy controls. This study reintroduced the concept of dysregulation in the “bladder–brain dialogue,” pinpointing the relationship between an overactive bladder and the ability to arouse the cortex, reporting differences in the sleep macrostructure of enuretic subjects, such as different representations of early stages of nonrapid-eye-movement sleep and a high rate of awakenings per hour.<sup>52</sup>

These findings tend to suggest the role of the arousal system in PNE pathogenesis; specifically, the small area around the locus coeruleus in the upper pons has been confirmed as playing a key role in PNE in some reports based on the activity of the autonomic nervous system.<sup>53,54</sup> From this point of view, our results about the higher prevalence of all sleep disturbances in an enuretic sample (SDSC total score,  $P \leq 0.001$ ), particularly in SHY ( $P \leq 0.001$ ) and respiratory troubles during sleep (SBD,  $P \leq 0.001$ ) could be interpreted as an epiphenomenon of autonomic nervous system activity. Conversely, it has been suggested that SRBD (particularly in the case of sleep apnea) may result in nocturnal diuresis mediated by atrial natriuretic peptide and antidiuretic hormone.<sup>46</sup> In fact, conditions of negative intrathoracic pressure as a result of inspiratory effort posed against a closed airway may result in the release of atrial natriuretic peptide due to cardiac distension caused by the negative pressure environment. Consequently, this hormone could increase water excretion and inhibit both vasopressin and the renin–angiotensin–aldosterone complex, which are involved in fluid volume regulation. In this light, the higher rate of SRBD in enuretic children when compared to healthy controls could be explained, even when considering the exclusion of obese subjects in our study sample.

In addition, there is observational evidence to suggest that PNE has been found to occur after psychological stress or trauma, and that PNE results in increased psychological distress for the child;<sup>55–57</sup> this suggests a putative role in the pathogenesis of DIMS, which was reported in our sample. Finally, Gozmen et al,<sup>58</sup> in 2008, reported that children affected by enuresis tend to have a worse sleep quality when compared to unaffected children.

We should take into account some limitations of this study. Our data were derived from parental questionnaires

and not from polysomnographic data and, therefore, the accuracy of our findings in evaluating sleep disturbances is limited. We could hypothesize that the parents of enuretic children could be used to checking their children during sleep in order to search for wetting episodes and to wake them more than parents’ of typical developing children. In this way, we may speculate that parents of enuretic children may pay more attention to the children’s sleep habits when compared to other parents.

In spite of these limitations, our study shows that among bedwetters, sleep could be strongly altered, thus affirming the hypothesis that PNE tends to alter the sleep architecture of affected children, or it could itself be the consequence of an abnormal sleep structure. In addition, the findings also pointed to the existence of a potential increase in the risk of developing sleep disorders in the presence of PNE, suggesting a new way to consider the relationship between sleep and enuresis in children.

## Disclosure

The authors report no conflicts of interest in this work. None of the authors has any personal or financial support or involvement with organizations that hold financial interest in the subject matter.

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