

## Possible Impact of Comorbid Conditions on the Persistence of Nocturnal Enuresis: Results of a Long-Term Follow-up Study

Pietro Ferrara,<sup>1</sup> Maria Chiara De Angelis,<sup>2</sup> Olga Caporale,<sup>2</sup> Monica Malamisura,<sup>2</sup> Valentina Del Volgo,<sup>2</sup> Flaminia Vena,<sup>2</sup> Antonio Gatto,<sup>1</sup> Antonio Chiaretti<sup>1</sup>

<sup>1</sup>Institute of Pediatric,  
Catholic University of  
Sacred Heart, Rome, Italy.

<sup>2</sup>Campus Bio-Medico Uni-  
versity, Rome, Italy.

Corresponding Author:  
Pietro Ferrara, MD  
Institute of Pediatric,  
Catholic University of  
Sacred Heart, Rome, Italy.

Tel: +39 06 30154348  
Fax: +39 06 3383211  
E-mail: pferrara@rm.uni-  
catt.it

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**Purpose:** To describe the natural history of patients with nocturnal enuresis (NE) during a 10-year period and to evaluate possible impact of comorbid conditions on the persistence of NE.

**Materials and Methods:** Ninety-five children (male to female ratio [M:F] 65:30), aged at first visit between 6 and 21 years were included in this study. Of study subjects 75 had primary monosymptomatic nocturnal enuresis (PMNE), 3 had secondary monosymptomatic nocturnal enuresis (SMNE) and 17 had non-monosymptomatic nocturnal enuresis (NMNE). Demographic and NE-related details were assessed from electronic medical records and by telephone interview at the times 3, 6, 12 months and 3, 5, 10 years after the first examination. Sixty-seven of 95 patients were enrolled, of whom 57 had PMNE (M:F ratio 39:18, mean age  $9.35 \pm 2.81$  years, mean age at improvement  $11.5 \pm 4.08$  years), 8 had NMNE (M:F ratio 4:4, mean age  $10.1 \pm 2.64$  years, mean age at improvement  $12.6 \pm 1.68$  years) and 2 had SMNE (M:F ratio 1:1, mean age 12 years, mean age at improvement  $13.5 \pm 2.12$  years).

**Results:** The mean duration of follow up was  $7.2 \pm 2.5$  years. All of the 67 children had 5 years follow up. Only 29 of 67 patients (19 with PMNE, 8 with NMNE and 2 with SMNE) had 10 years follow up and 4 of 19 with PMNE were still affected by NE. Out of 57 patients with PMNE 12 (2/12 with language disorders, 1/12 varicocele and 1/12 cryptorchidism) and out of 8 patients with NMNE 1 were still enuretic while all patients with SMNE were in remission.

**Conclusion:** We observed that language disorders and testicular pathology in NE children could be comorbidities associated with persistence of NE and treatment resistance.

**Keywords:** nocturnal enuresis; risk factors; comorbidity; epidemiology; urination disorders.

## INTRODUCTION

According to International Children's Continence Society (ICCS), nocturnal enuresis (NE) is defined as intermittent incontinence while asleep in children older than 5 years age in which the sphincters control is acquired.<sup>(1)</sup> Night wetting is dichotomized into monosymptomatic NE (MNE) and non-monosymptomatic NE (NMNE).<sup>(2)</sup> MNE means bedwetting without any other lower urinary tract symptom (LUTS), and without a history of bladder dysfunction. NE in children with any other LUTS and with a history of bladder dysfunction is defined as non-monosymptomatic nocturnal enuresis (NMNE).<sup>(1,2)</sup>

There are different types of MNE including primary monosymptomatic nocturnal enuresis (PMNE) diagnosed in child who has never achieve nocturnal urinary continence (UI) and has never been dry at night.<sup>(3)</sup> It is considered related to impaired sleep arousal, to nocturnal polyuria, to a small nocturnal bladder capacity, or to a combination of these factors. Secondary monosymptomatic nocturnal enuresis (SMNE) describes children who acquired urinary continence for at least 6 months and it is usually secondary to psychological stress or organic causes.<sup>(4)</sup>

Categorization into MNE and non-MNE, based on the absence or presence of bladder dysfunction, respectively, is important in clinical practice.<sup>(5)</sup> The estimated prevalence of NE are highly variable<sup>(6)</sup> because there is a heterogeneity in diagnostic criteria with few studies using ICCS standardization.<sup>(1)</sup> The study of Nevés and Sillén described the prevalence of NE and UI as approximately 10-15% at 5-year old, 5-10% at 7-year old, 3-8% at 10-year old children and 1-4% in adolescents with 0.5-2% in the untreated adults.<sup>(7)</sup>

Bedwetting is more common in boys than girls until the teenage years.<sup>(8)</sup> Most studies show decreasing prevalence with increasing age, until about 1-2% in adulthood.<sup>(9)</sup>

NE is a multifactorial disorder with a genetic underpinning. Butler described a conceptual model that NE occurs when there is poor arousal from sleep in response to a sensation of a full bladder associated with overactivity of bladder function or with an excessive overnight urine production, or both.<sup>(10)</sup>

Other risk factors and correlates of NE include, delay in attaining bladder control, physiological factors such as constipation, fecal incontinence, daytime UI, caffeine consumption, sleep apnea, upper airway obstructive symptoms, lower socioeconomic status and black race.<sup>(6,11,12)</sup>

Family history of NE, is positive in 50% of cases. In particular PMNE may be polygenetic, candidate genes have been localized to chromosomes 13, 12 and 8.<sup>(4,13)</sup>

Although different treatments (pharmacological, psychological/behavioral and alternative interventions) have been tried for NE, the relative effectiveness of each one remains uncertain. Simple behavioral interventions are often the first line treatment tried by parents or caregivers at home with minimal professional involvement, including the reduction fluid intake after 6 or 7 pm and motivational

therapy with a chart for dries nights. Active treatment should be avoided in children < 6 years of age.

The first line therapy for the subgroup of patients with PMNE associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP) and/or the NE alarm (both level 1 grade A recommendations).<sup>(1,14,15)</sup> dDAVP is an effective treatment for PMNE, it rapidly reduces the number of wet nights per week compared with placebo and with homotoxicological remedies.<sup>(16)</sup> Recent guidelines recommend an individualized treatment based on parameters obtained using a voiding diary.<sup>(17)</sup> Therefore, it is important to identify effective interventions because successful treatment of NE can result in improvement in health, self-esteem and quality of life.<sup>(11)</sup>

The aim of this study is to evaluate the natural history of patients with NE investigating a 5 and 10-year follow up period to increase the knowledge on these conditions in particular the possible impact of comorbid conditions on the persistence of NE.

## MATERIALS AND METHODS

### Study Subjects

Children with NE and/or LUTS who referred to the Pediatric Nephrology Clinic of "A. Gemelli" University Hospital of Rome between January 2000 and December 2008 were eligible for inclusion in the study. Exclusion criteria were, urogenital malformations, renal failure and chronic disease such as diabetes. We analyzed retrospectively data on medical records to identify signs and symptoms of voiding disorders and to evaluate behavioral characteristics of the child during the first examination and then by telephone interview which were performed at follow up periods of 3, 6 12 months and 3, 5 10 years.

Demographic details (sex, age) at first observation, family history of NE, age at attaining diurnal continence, and characteristics related to bedwetting, e.g. frequency of wetting, daytime incontinence, urgency, wetting during the early hours of sleep (before 12 pm) and early hours of morning (after 12 pm), deep sleep, snoring, left-handedness,<sup>(18)</sup> previous surgery, lumbosacral region trauma, allergies, constipation, encopresis, urinary tract infection (UTI), previous therapy, presence of stress and worrying events including socialization and school performance, polythelia and signs of spinal dysraphism,<sup>(19)</sup> were extracted from patients' records. To diagnose constipation, we used the Rome III criteria. At least two of the following criteria must be met for  $\geq 2$  months before diagnosis (patients should not have a diagnosis of irritable bowel syndrome),  $\leq 2$  defecations in the toilet per week,  $\geq 1$  episode of fecal incontinence per week, history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, presence of a large fecal mass in the rectum and history of large diameter stools that may obstruct the toilet. Of the 95 eligible patients, 67 (male to female ratio [M:F] of 44:23, mean age at first visit  $10 \pm 2.78$  years) participated in the telephone interview and were included in the study. Age of im-

provement, compliance to treatment and length of treatment were assessed by telephone interview at the follow up times of 3, 6 12 months and 3, 5 10 years after the first visit.

Using ICCS definitions of PMNE (child who has never achieve nocturnal urinary continence and has never been dry at night), SMNE (child who has acquired control for at least 6 months and it is usually secondary to psychological stress or organic causes) and NMNE patients were included in 3 groups.

Of the 67 eligible patients there were 57 children with PMNE, 39 (68.4%) male and 18 (31.6%) female with mean age at first examination  $9.35 \pm 2.81$  years; 2 with SMNE, 1 (50%) male and 1 (50%) female, they were both 12 years old at first observation and 8 children with NMNE, 4 (50%) male and 4 (50%) female with mean age at first observation  $10.12 \pm 2.64$  years.

Data referring to the treatment response were classified as follows: “partial response” as a reduction of wet nights of 50-90%, and “full response” as a reduction of at least 90%.

### Statistical Analysis

Data are presented as frequency, percentage and standard deviation. Comparison of remission in patients who received and didn't receive special treatments is analyzed using chi-square test and  $P < 0.05$  was considered statistically significant. The same statistical method is used to analyze data on positive family history.

## RESULTS

Ninety-five children were eligible for the study, 75/95 (78.9%) with PMNE, 17/95 (17.9%) with NMNE and 3/95 (3.2%) with SMNE. Of the 75 eligible children with PMNE, 57 (76.0%) had completed interviews and agreed to give information, while 13 (17.3%) did not participate due to disconnected telephone number and 5 (6.7%) didn't participate due to parental refusal, parents affirmed that their children had never suffered from NE. Eight of 17 (47.0%) patients with NMNE and 2/3 (66.7%) with SMNE participated in the telephone interview.

The characteristic of the 57 patients with PMNE were: mean age at remission  $11.5 \pm 4.08$  years; positive family history for NE 39/57

(68.4%); constipation 3/57 (5.2%); left-handedness 12/57 (21%); deep sleep 53/57 (92.9%); UTIs 3/57 (5.2%) and polythelia 6/57 (10.5%). Thirty of 57 (52.6%) children were treated with dDAVP; 10/30 (33.3%) with nasal spray, 13/30 (43.3%) oral tablets 0.2 mg and 7/30 (23.3%)

oral dDAVP lyophilisate 120 µg (MELT). The characteristics of these patients group were M:F ratio of 23:7; mean age at first examination  $9.6 \pm 2.6$  years and mean age at remission  $11.8 \pm 3.73$  years. At the different follow-up times the percentages of remission in children with drug therapy were 16/30 (53.3%) at 3 months; 18/30 (60.0%) at 6 months; 18/30 (60.0%) at 1 year; 19/30 (63.3%) at 3 years and 23/30 (76.7%) at 5 years. At 10 years we had data only for 12/30 children; 9/12 (75.0%) were in remission and 3/12 (25.0%) had PMNE (Table 1). Of these patients, 2/12 (16.7%) were affected by language disturbances, 1/12 (8.3%) had dyslexia, 1/12 (8.3%) had delayed language development, 1/12 (8.3%) child had varicocele and another 1/12 (8.3%) had cryptorchidism. Among 3 patients still bedwetting, 1 was affected by dyslexia, 1 had delayed language development and cryptorchidism and 1 was affected by varicocele.

Twenty-seven of 57 (47.4%) children were never treated with pharmacologic therapy, M:F ratio of 16:11, mean age at first examination  $9.0 \pm 2.9$  years and mean age at remission  $11.6 \pm 4.47$  years. At the different follow up time the percentage of remission in untreated children were 3/27 (11.1%) at 3 months; 4/27 (14.8%) at 6 months; 8/27 (29.6%) at 1 year; 19/27 (70.4%) at 3 years and 22/27 (81.5%) at 5 years. At 10 years we had data only for 7/27 children; 6/7 (85.7%) were in remission and 1/7 (14.3%) had PMNE.

The rate of remission in 39/57 (68.4%) children with PMNE and positive family history was 12/39 (30.8%) at 3 months, 15/39 (38.5%) at 6 months; 21/39 (53.9%) at 1 year; 27/39 (69.2%) at 3 years and 32/39 (82.1%) at 5 years. At 10 years we had data only for 12 patients and

rate of remission not considered.

The rate of remission in children without family history of NE 18/57 (31.6%) was 4/18 (22.2%) at 3 months; 5/18 (27.8%) at 6 months; 7/18 (38.9%) at 1 year; 11/18 (61.1%) at 3 years and 13/18 (72.2%) at 5

**Table 1.** Characteristics of treated and untreated children with primary monosymptomatic nocturnal enuresis.

Variables	Therapy	No therapy	P Value
Patients (no.)	30	27	----
Male	23	16	----
Female	7	11	----
Mean age at first visit (years)	9.6	9.0	----
Mean age at remission (years)	11.8	11.6	----
Remission at (%)			----
3 months	53.3	11.1	.0007
6 months	60.0	14.8	.0005
1 year	60.0	29.6	.02
3 years	63.3	70.4	.57
5 years	76.7	81.5	.65
10 years	75.0	85.7	.58

years. At 10 years we had data only for 7 patients and rate of remission was not considered (**Table 2**).

Of the 17 children affected by NMNE, 8 had completed telephone interview: 4/8 (50%) had positive family history, 6/8 (75%) had deep sleep and none had UTI or left-handedness. Mean age at recovery was  $12.6 \pm 1.68$  years. Pharmacological treatment was administered for 4/8 children (50%). The characteristics of this group were: M:F ratio of 3:1; mean age at first examination  $9.7 \pm 2.21$  years and mean age at remission  $12.7 \pm 0.95$  years. At the different follow up points the percentage of remission were 1/4 (25%) at 3, 6 and 12 months; 3/4 (75%) at 3 and 5 years and 4/4 (100%) at 10 years. At 10 years follow up, all the patients were in remission. One had a complete remission after 1 month of therapy, 2 had a partial response until the complete remission after 3 years, 1 child didn't respond to therapy but he had a complete remission after 6 years spontaneously. Four of 8 children, M:F ratio of 1:3, with NMNE were never treated with drug therapy, mean age at first visit was  $10.25 \pm 3.31$  years; mean age at recovery was  $12.5 \pm 2.38$  years. At the follow-up after 3, 6 and 12 months and after 3, 5 and 10 years from the first visit, the percentage of remission were at 3 months 1/4 (25%); at 6 months 1/4 (25%); at 1 year 2/4 (50%); at 3 years 3/4 (75%); at 5 years 4/4 (100%) at 10 years 4/4 (100%).

Of the 3 children with SMNE, 2 completed telephone interview, 1 was male, who was never treated with pharmacologic therapy and had a complete remission after 3 years spontaneously; the other 1 was female, she was treated with MELT with a full response and complete remission after 1 month of therapy. At the follow up after 5 and 10 years, both of them were in remission.

## DISCUSSION

According to other studies, our results confirm the recurrence of positive family history for NE. Approximately 32% of cases are sporadic and 68% seems to follow a genetic predisposition. Many authors had identified some associated genetic loci on different chromosomes, mainly a gene on chromosome 13 responsible for the dominant inheritance of NE and a gene on chromosome 12, on 22 and probably on 8.<sup>(4,13)</sup> Thus, molecular genetics have shown that NE is a genetically complex disorder with locus heterogeneity and presumed gene-environment interactions.

Von Gontard and colleagues and Wang and colleagues demonstrated that a positive family history had significant effects on the children

with PMNE, in particular, children with familial aggregation PNE are more likely to be severe symptoms and bladder dysfunction.<sup>(20,21)</sup> Our study instead showed that at 5 years of follow up 82% of children with family history for NE were in remission vs. 72.2% of whom without family history of NE and the same trend was also observed in all previous follow up. These data could be analyze considering the association between genotype and phenotype to evaluate eventually genotype associated with the persistence of enuresis.

In our study we observed that the highest percentage of remission (33.3%) occurred in the age group of 9-11 years and that, also among children who had never received pharmacologic therapy, 48.2% achieve spontaneous remission between 9-11 ages. However, details on reasons of this age distribution of remissions remain unknown. We observed that only 5.2% of children with PMNE presented constipation, despite of previous studies which showed that prevalence of constipation in children affected by NE was significantly higher (12.6%).<sup>(22-24)</sup> Furthermore, in our study, none of the children who were still affected by NE at 5 and 10 years had constipation. Our study also showed an interesting relationship between oral language disorders and NE; 2/12 children who, after 10 years from the first visit, were still affected by NE, presented oral language disorders, dyslexia in one case and delayed language development in the other case. According to several studies the frequency of language disorders in the general population varied from 10-15% at 2 years old to 3% at 5 years old. This association at 10 years follow up was very strong so also considering the limit of small size of our study population this data is very significant. These data indicate that enuretic children present a higher percentage of oral language disorders when compared to non-enuretic children.<sup>(25)</sup>

Previous researches have instead suggested the association between NE and attention deficit hyperactivity disorder (ADHD), probably related to delays in central nervous system maturation.<sup>(26)</sup> Comorbidity between NE and ADHD could either be due to common etiologic pathways underlying these two conditions or due to "causal" relations in which the non-resolution or treatment of one disorder increases the risk for the other disorder.<sup>(27)</sup>

There aren't data that showed a correlation between NE and testicular pathology, while we had observed that 2 children with long-term NE presented this kind of problems: cryptorchidism in a case and varicocele in another one.

**Table 2.** Rate of remission in children with and without family history of nocturnal enuresis.\*

Follow up Periods	Children with Positive Family History	Children without Family History	P Value
3 months	30.8	22.2	.50
6 months	38.5	27.8	.43
1 year	53.9	38.9	.29
3 years	69.2	61.1	.54
5 years	82.1	72.2	.39
10 years	75	85.7	.58

\* Data are presented as percentage.

## CONCLUSION

Considering the possible correlation between language disorders, testicular pathology and long term NE, it could be suggested that pediatricians, when dealing with this kind of diseases in enuretic children, pay more attention to the NE treatment, in a bio-psychical approach. Future investigations on larger sample are useful to clarify this hypothesis. If this association will be confirmed the treatment in this children could be more strong both in drug and motivational therapy.

## CONFLICT OF INTEREST

None declared.

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