



# Innocent heart murmurs and enuresis: Examining a possible link

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## ABSTRACT

**Objective:** The aim of this study was to evaluate the prevalence of innocent heart murmurs in children affected by nocturnal enuresis (NE).

**Material and methods:** We enrolled a total of 401 children (G1), 300 males and 101 females, aged 5–15 years, affected by NE and referred to the Service of Pediatrics, “Campus Bio-Medico” University Hospital of Rome, from September 2013 to September 2018, into the study. The control group was composed of 394 children without NE (G2). The study was carried out in compliance with the Helsinki Declaration.

**Results:** The prevalence of innocent heart murmurs in G2 was 6.34%. This condition was significantly more frequent in children who suffered from NE. Indeed, in G1, the prevalence of innocent heart murmurs was 21.45%, although there were few differences between the children with monosymptomatic NE and non-monosymptomatic NE; moreover, this prevalence was higher in males.

**Conclusion:** These findings made us aware of the presence of possible underlying mechanisms, which explain the association between a higher prevalence of innocent heart murmurs and enuresis, and further studies are required to explore this issue.

**Keywords:** Child; innocent heart murmur; nocturnal enuresis.

## Introduction

Nocturnal enuresis (NE) is a very common clinical disorder with a profound impact on affected children and their families. NE is defined as repeated voiding, accidental or on purpose, into clothing or the bed, at least twice a week, for three consecutive months, in children older than 5 years, the age by which the sphincter control should be acquired, according to the International Children’s Continence Society recommendations (ICCS).<sup>[1]</sup> NE is a multifactorial disorder. It has three main pathophysiological determinants: nocturnal polyuria, the detrusor overactivity, and failure to awaken in response to bladder sensations. Other risk factors that are shown to be associated with NE include a family history, delay in attaining bladder control, sleep disorders, male gender, attention deficit/hyperactivity disorder (ADHD), low socioeconomic status, caffeine consumption, poor school performance, and

constipation or fecal incontinence.<sup>[2-4]</sup> NE is divided into monosymptomatic (MNE) in children without any other lower urinary tract symptoms and without a history of bladder dysfunction, and into non-monosymptomatic (N-MNE), which is accompanied by daytime urinary symptoms. These two types are pathogenetically and clinically different, so they require different modalities for management.

Innocent heart murmurs is a benign physical finding related to the flow across normal cardiac structures, which needs to be distinguished from pathological auscultatory sounds, the signals of underlying cardiac abnormalities. Nevertheless, it can be very difficult to make a distinction during a physical examination, and it is necessary to focus on features such as the timing, location, quality, and loudness.<sup>[5]</sup>

Innocent heart murmurs may occur transiently in some children, based on their size, age, and hemodynamic state at the time of the examination.

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The aim of the study was to evaluate the prevalence of the innocent heart murmur in children affected by NE vs. the control group. Specifically, for this purpose, a possible pathogenic relationship link both conditions.

## Material and methods

We enrolled a total of 401 children (G1), 300 males and 101 females aged 5–15 years, affected by NE and referred to the Service of Pediatrics, “Campus Bio-Medico” University Hospital of Rome, from September 2013 to September 2018. To be eligible for inclusion, patients had to meet the ICCS classification of NE. Exclusion criteria were secondary NE, a history of urinary tract infections, other urinary tract disorders, and other pharmacological treatments within the past 3 months. We separately assessed children with MNE from children with N-MNE.

The control group was composed of a total of 394 healthy children without the NE diagnosis (G2). In particular, G2 included 205 males and 189 females aged 5–15 years, enrolled in a pediatric general service during a routine health check-up.

The study was characterized by a careful examination of patient’s medical history and performing of physical examination, including the weight and height measurement. Mostly, it was a cardiological examination including monitoring patient’s blood pressure and abnormal heart sounds: patent’s foramen ovale, slight systolic impurity, mitral insufficiency, muffled heart sound, heart murmur, and impurity. The study was carried out in compliance with the Helsinki Declaration and was approved by the Service of Pediatrics of “Campus Bio-Medico” University, Rome.

## Statistical analysis

Analyses were conducted using the Microsoft Excel 2011 (version 14.0.0) program. We used descriptive statistics to describe patients’ information (age, gender, familiarity). Data were expressed as the mean±standard deviation and percentage. The  $\chi^2$  test was used for categorical variables. The significance level was set at  $p<0.05$ .

## Results

In the G1 group, a total of 327 patients suffered from MNE, and 74 patients were afflicted with N-MNE. The G1 group was composed of 300 males (74.81%) and 101 females (25.19%) aged 5–15 years (the mean age, 8.49 years). In particular, the male mean age (9.05 years) was 1.12 years higher than the female mean age (7.49 years).

The group of children that suffered from MNE consisted of 242/327 males (74.01%) and 85/327 females (25.99%), and the other group (N-MNE) was composed of 58/74 males (78.38%) and 16/74 females (21.62%).

During the cardiological physical examination, carried out by a pediatrician, we observed that 48/327 males (14.68%) and 18/327 females (5.50%) from the MNE group presented with innocent heart murmurs; 15/74 males (20.27%) and 5/74 females (6.76%) from the N-MNE group presented with innocent heart murmurs (Table 1). We conducted an accurate anamnesis, and in some cases, we proposed an echocardiography, but in this study, we enrolled only children with innocent heart murmurs, without any other heart disease.

In the G1 group the prevalence of innocent heart murmurs was 21.45% (86/401). In particular, in 63/300 males (21%) and 23/101 females (22.77%), we observed innocent heart murmurs.

On the other hand, the G2 group included 205 males (52.03%) and 189 females (47.96%) aged 5–15 years. During the physical

**Table 1. Prevalence of innocent heart murmurs in children with MNE or N-MNE**

	MNE (n=327)	N-MNE (n=74)
Males	14.68% (48/327)	20.27% (15/74)
Females	5.50% (18/327)	6.76% (5/74)
Total	20.18% (66/327)	27.03% (20/74)

MNE: monosymptomatic nocturnal enuresis; N-MNE: non-monosymptomatic nocturnal enuresis

**Table 2. Prevalence of innocent heart murmurs in children**

	Children with NE (MNE+N-MNE) (n=M+F=401)		Children without NE (n=M+F=394)		p
	Males (n=300)	Females (n=101)	Males (n=205)	Females (n=189)	
Total (Males+Females)	21% (63/300)	22.77% (23/101)	7.31% (15/205)	5.29% (10/189)	<0.001

NE: nocturnal enuresis; MNE: monosymptomatic nocturnal enuresis; N-MNE: non-monosymptomatic nocturnal enuresis

examination, it was noted that 15 males (7.31%) and 10 females (5.29%) had innocent heart murmurs in this group. In the G2 group, the prevalence of innocent heart murmurs was 6.34% (25/394).

Considering these data, we found that the prevalence of innocent heart murmurs was significantly higher in G1 vs. G2 (21.45% vs. 6.34%;  $p < 0.001$ ) (Table 2).

## Discussion

A number of studies examined the relationship between NE and other conditions. Indeed, there are studies that investigated allergic rhinitis and the associated risk with NE in children: Children with allergic rhinitis had a higher incidence and subsequent risk of NE.<sup>[6]</sup>

In other studies, NE in children with asthma was examined. These studies showed that the prevalence of NE in children with asthma was higher than in same-age controls.<sup>[7]</sup> Moreover, they considered the association between NE, the body weight, and obstructive sleep apnea in children.<sup>[8]</sup>

In addition, NE is an incidental finding in children diagnosed with ADHD. The therapy of ADHD is directed to the neuro-behavioral problem using specific drugs and therapies, which are also resolute in the enuretic disorder.<sup>[9]</sup> Some studies investigated a possible pathogenic link between headache, migraine, and nocturnal enuresis in children.<sup>[10]</sup> In addition, the prevalence of left-handedness was significantly higher in children with NE than in healthy children.<sup>[11]</sup> To the best of our knowledge, there have been no studies investigating the association of NE with innocent heart murmurs in the literature.

Based on our data, we could only speculate about the underlying mechanisms of the association between a higher prevalence of innocent heart murmurs and NE. A possible explanation for this relationship could be provided by an increased secretion of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (B-BNP). In particular, the murmur is due to the blood flowing in the cardiac structures, and it can be accentuated by hypervolemia, which in turn determines the atrial and ventricular distention. This stimulates cardiomyocytes into producing the ANP and B-BNP. The ANP shares with B-BNP a high degree of structural homology and a profile of diuretic, natriuretic, and vasodilatory activities and inhibition of the renin-angiotensin-aldosterone system.<sup>[12]</sup> The kidney is one of the main target organs for natriuretic peptides. It has natriuretic peptide receptors predominantly in the glomeruli and inner medulla; moreover, it has also been reported that the kidney itself produces ANP.<sup>[13,14]</sup> These hormones acting on the kidney cause an increase in the urinary production, which leads to NE.

Moreover, some foods and beverages can promote diuresis or detrusor overactivity, which in some people can exacerbate the overactive bladder symptoms and NE. These findings explain how behavioral therapy by reducing the consumption of foods and drinks containing caffeine, carbonated drinks, and fluid intake after 6 p.m. (or approximately 3–4 h before bedtime) can often promote continence.<sup>[15]</sup> Therefore, dietary changes and behavioral interventions are usually recommended in NE to reduce the fluid intake before bedtime, to reduce the consumption of carbonate drinks, and to treat constipation. However, most dietary advices to treat NE are non-specific and are provided before the beginning of therapy. Fluid restriction reduces the total overnight urine production, which reduces the child's need to void overnight.

Innocent heart murmurs are caused by the blood flowing through the heart and vessels that branch out of it, in the absence of anatomical or functional abnormalities. The most common innocent heart murmur is an ejection systolic murmur with medium tonality, vibratory or “musical,” heard better along the lower and the middle left sternal margin, without a significant irradiation at the apex, at the base or the back; moreover, it varies passing from orthostatism to clinostatism. It is most frequently found in children aged 3–7 years, and it often disappears spontaneously as children grow up. Moreover, it is important to investigate the presence of innocent heart murmurs in childhood because they are often associated with increased parental concern.<sup>[16]</sup> Indeed, parents are frightened when they first hear the word “murmur” from their primary care physicians. Therefore, parents start unnecessarily restricting their children from the physical activity, and they also think of the murmur as a heart disease that is going to affect their child's entire life, so they should be reassured that their children with benign murmurs do not have any underlying structural heart disease.

In conclusion, a possible correlation between innocent heart murmurs and NE could suggest that pediatricians should pay more attention to the NE approach. Future investigations including a larger sample would be useful in clarifying this hypothesis.

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**Ethics Committee Approval:** The study was carried out in compliance with the Helsinki Declaration and was approved by the Service of Pediatrics of Campus Bio-Medico University, Rome.

**Informed Consent:** Written informed consent was obtained from the parents of the patients who participated in this study.

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

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