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ORIGINAL ARTICLE

Impact of a multidisciplinary evaluation in pediatric patients with nocturnal monosymptomatic enuresis

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Abstract

Background Enuresis (NE) is a clinical condition of multifactorial etiology that leads to difficulties in child/adolescent social interaction.

Methods This was a prospective study on the impact of multidisciplinary assessment of 6- to 17-year-old patients with monosymptomatic nocturnal enuresis (MNE), including a structured history, clinical/neurological examination, bladder and bowel diaries, sleep diary and questionnaires, psychological evaluation [Child Behavior Checklist (CBCL) and PedsQL 4.0 questionnaires], urinary sonography, blood and urine laboratory tests, polysonography (PSG), and balance evaluation.

Results A total of 140 enuretic participants were evaluated, of whom 27 were diagnosed with NE complicated by urinary disorder, four with hypercalciuria, three with nephropathy and one with attention-deficit hyperactivity disorder. Among the 87 participants who underwent PSG, six were diagnosed with severe apnea. Of the 82 MNE patients who underwent full assessment, 62 were male (75.6 %), and the mean age was 9.5 (±2.6) years. A family history of NE was diagnosed in 91.1 % of first- and second-degree relatives, constipation in 89.3 % and mild/moderate apnea in 40.7 %. Balance control alteration was identified by physical therapy evaluation of MNE patients. Participants' quality of life evaluation scores were significantly lower than those of their parents.

Conclusion Enuresis is a multifactorial disorder that requires a structured diagnostic approach.

Keywords Monosymptomatic nocturnal enuresis · Children · Adolescents · Multidisciplinary assessment · Physiotherapy · Psychology

Introduction

Monosymptomatic nocturnal enuresis (MNE) can be defined as the presence of urine incontinence during sleep, in the absence of daytime symptoms, in toilet-trained children of at least 5 years of age. Primary MNE is manifested by episodes

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of bedwetting since the acquisition of bladder control, while secondary MNE is characterized by urine incontinence during sleep after full bladder control has been acquired for at least six months [1, 2]. The concept of MNE infers the absence of functional or chronic conditions as causes of nocturnal urine loss. Enuresis (NE) affects approximately 10 % of 7-year-old children and 1–2 % of adolescents and young adults, with familial occurrence in most affected patients [3, 4].

MNE has been considered to result from a pathogenic triad that includes a lack of vasopressin secretion during sleep, instability and/or reduction of nocturnal bladder capacity and inability to awaken by the sensation of a full bladder [5]. It is recognized that a series of comorbid medical conditions [6] and behavioral changes, including such disorders as attention-deficit hyperactivity disorder (ADHD) [7] and opposition de-fiant disorder [8], can present as nocturnal enuresis, while MNE can be adversely affected by the coexistence of other conditions, such as the presence of constipation [9] and sleep apnea [10], among others. Immaturity of the nervous system in terms of bladder function regulation has been suggested as an etiological factor of MNE [11]. However, regarding MNE, the developmental delay does not seem to be specific to blad-der control, since children with MNE and nocturnal enuresis with daytime symptoms present immature motor performance skills, with losses in fine and global motor function, slower motor performance particularly for repetitive hand and finger movements [12], reduced ability of visual–motor and spatial perception, dysarthria and incoordination [13], suggesting a maturation deficit in the motor cortex circuits and related cor-tical areas and a possible postural control deficit.

MNE is a multifactorial entity in which the genetic factor seems to be of great importance while the environmental, somatic and psychosocial factors play a modulatory role [3, 7]. Despite the advances in acknowledging the multiple fac-tors that may play a role in the physiopathology of MNE, the need for patient evaluation by a multidisciplinary team has been rarely addressed in the literature [14]. In the study pre-sented here, we used a multidisciplinary evaluation of children and adolescents with NE to differentiate, at presentation, MNE, non-monosymptomatic enuresis (NMNE) and enuresis associated with underlying chronic diseases, as well as to rec-ognize comorbidities. The aim of applying this approach was to establish a multidisciplinary evaluated cohort of patients with MNE for future follow-up with specific therapeutic interventions.

Methods

This was a prospective study conducted from August 2011 to December 2012 by a multidisciplinary team involving the Pediatric Nephrology and Sleep Physiology Units of Instituto da Criança of Hospital das Clinicas of the

University of São Paulo Medical School, the University of São Paulo Physical Therapy Division and the Behavioral Therapy Unit of the Department of Psychology of the University of São Paulo. A structured protocol was applied to identify patients with MNE. The inclusion criteria were: age between 6–17 years and MNE diagnosis according to the "International Children's Continence Society" (ICCS) criteria [1, 2], which determine that incontinence should be exclusive-ly nocturnal. In addition, the present cohort included only patients without previous urinary incontinence during the day.

Patients were recruited using digital media, AM/FM radio interviews and articles in newspapers and magazines. After registration, interested patients and their families received a questionnaire by mail which focused on socioeconomic as-pects [15] and an inventory for behavior assessment of 6- to 18-year-old participants [Child Behavior Checklist (CBCL)] [16, 17].

The socioeconomic profile of the study participants was evaluated by the "Critério Brasil" questionnaire [15], which evaluates the degree of education of the head of the household and a number of household characteristics, such as presence and quantity of specific comfort items. The questionnaire awards points depending on household characteristics and re-sults in an economic classification defined as social classes A1, A2, B1, B2, C1, C2, D and E.

The CBCL has been validated in Brazil and it is composed of 130 questions related to the social competence and behavior patterns of 6- to 18-year-old individuals in the last six months, as observed by parents. The questionnaire was designed to be answered in a maximum of 15 minutes and uses scores to enable clinical comparison: the child/adolescent profile is assessed in relation to their overall operation, internalizing profiles (including isolation issues, somatic complaints, anxiety/depression) and externalizing profiles (including violation of rules and aggressive behavior). For the present study a cut-off score of 60 was used; participants who scored above that cut-off were classified as borderline or clinical cases, and considered as a group, as recommended by Achenbach and Rescorla for research using the CBCL [17].

All participants who returned a completed CBCL were invited to an initial clinic visit in which, after signing an in-formed consent form, they were evaluated sequentially by a pediatric nephrologist, a pediatric neurologist, a physical ther-apist and a psychologist. Anamnesis was structured according to ICCS recommendations [1, 2] and followed by a complete clinical examination, completion of sleep disorders question-naires (Berlin Questionnaire, Children's Sleep Disorders Scale and Epworth Scale) [18–20], evaluation of balance and com-pletion by patients and their caregivers of a quality of life questionnaire [Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0)] [21].

The neurological examination included perinatal history, evaluation of potential risk factors for neurological conditions,

cognitive assessment (adequacy of responses and simple calculations, abstraction), static and dynamic balance, axial and appendicular coordination, muscle strength, bone-tendon reflexes and cranial nerve evaluation.

The physical therapy evaluation consisted of an assessment of balance. Balance is the ability to maintain body stability. Data were acquired using a system comprised of a force plate (EMG System do Brasil Ltda®, São José dos Campos, SP, Brazil) and an analogue digital convertor (OR6 12-bits) connected to a computer at a frequency of 100 Hz. A computerized program transformed the primary center of pressure (COP) signal into numeric data throughout the acquisition duration. COP is the point that results from the action of vertical forces projected onto the force plate. COP displacement reflects the body's movements in the attempt to keep the center of mass within the boundaries of the weight-supporting base (both feet) and maintain the body's balance. The children were asked to stand barefoot with their arms at their side on a force plate embedded in the laboratory floor and to remain motionless. Because integration of visual, somatosensory and vestibular information is essential for balance, data from 60 seconds (60-s) trials were collected under four different sensory conditions: (1) eyes open, standing on a stable surface, (2) eyes closed, standing on a stable surface, (3) eyes open, standing on an unstable surface and (4) eyes closed, standing on an unstable surface. A 60-s rest interval was allowed between each sensory condition trial [22].

At the end of the first visit, the participants were scheduled for complementary urine and blood tests, kidney and urinary tract ultrasound and polysonography (PSG). They were also given instructions to keep a diaries on fluid intake and urinary and bowel habits for seven days and on bedwetting frequency [1] and sleeping pattern [23] for 30 days.

A diaper was used in all patients during the PSG in order to characterize the nocturnal urine volume. Blood tests to evaluate complete blood count, urea, creatinine and venous blood gas were requested. Urine was initially evaluated by urinalysis and by the single-sample calcium/creatinine ratio. Urine culture was obtained if urinalysis suggested urinary infection. If the urinary calcium/creatinine ratio was ≥0.21, a 24-h urine calcium collection was performed (positive when ≥4 mg/kg in 24 h).

A full-night PSG was performed using an EMBLA N7000® recording system (Natus Medical Inc., Pleasanton, CA) with the capability for electroencephalogram (EEG), chin electromyogram (EMG), ocular electrodes (EOG), respiratory variables recording (nasal pressure cannula, thermistor, thoracic and abdominal belts for effort detection), left and right tibialis EMG, pulse and position sensors, peripheral oxygen saturation and snoring microphones. The sleep stage and respiratory, motor and cardiac events were scored following the 2012 American Academy of Sleep Medicine (AASM) specifications [23].

The morphology of the urinary system, bladder capacity, post-voiding residual urine (normal ≤20 ml) and bladder thickness (normal ≤3 mm) were evaluated by renal and urinary tract sonography [24]. A bladder volume of ≤65 % of expected bladder capacity for age identified a small capacity bladder, while a bladder volume of >150 % of expected bladder capacity for age identified an increased capacity bladder. Sonographic evaluation of the rectum transverse diameter was performed in sequence (normal <30 mm) as a tool for the diagnosis of constipation [2, 25].

ICCS criteria were used to characterize "nocturnal polyuria" [1], "frequent episodes" of NE were defined as ≥4 episodes of bedwetting per week [2]. Constipation was defined by anamnesis, as the elimination of hard stools with effort, pain or difficulty, soiling and bleeding around the stool, with or without increasing the interval between bowel movements [9]. Diagnosis of constipation was confirmed by the Rome III questionnaire [26], the Bristol stool scale [27], bowel diary and the rectum transverse diameter measurement by pelvic sonography [25].

At the end of the initial clinic visit, each participant and his/her caregiver, after receiving instructions from a designated psychologist, were asked to separately complete the PedsQL 4.0 [21] questionnaire (use of the PedsQL.4.0 was authorized by the institution which owns its copyright. As a general rule, this instrument takes 5 min to complete and has three models for application in three age groups, namely, 5–7 years, 8–12 years and 13–18 years, respectively. This instrument investigates problems that occurred in the last month in the areas of physical capacity (8 questions), emotional aspects (5 questions), social aspects (5 questions) and school activities (5 questions). Parents and participants are instructed to score "zero" when the presented issue "is never a problem", and to rate as "four" issues than "almost always constitute a problem". The resulting score is converted to a scale of 0 to 100, with higher values indicating a better quality of life.

After completion of the investigation, participants diagnosed with NMNE, MNE preceded by NMNE or enuresis associated with genetic syndromes or underlying chronic diseases, such as hypercalciuria, diabetes mellitus, diabetes insipidus, sickle cell anemia, urinary malformations, chronic kidney disease, severe sleep apnea, neurodevelopmental delay, convulsive syndromes or ADHD, were referred for a specialized evaluation.

Statistical analysis

Descriptive analysis was performed with the R computing program version 3.2.2, on a Mac OS X Yosemite (10.10.5) computer. Descriptive analysis of demographics, the history and clinical examination and laboratory tests, the structure of sleep, the results of the CBCL and PedsQL questionnaires and balance assessment was performed by calculating the

frequency for categorical variables and determining the median, mean and standard deviation for continuous variables. A significance level of 5 % (p <0.05) was adopted. Comparison of PedsQL 4.0 Scale scores between patients/parents was performed utilizing the paired Student's t test to compare means of scores. A level of significance of p < 0.05 was adopted.

Results

Interest in enrolling in the study protocol was manifested by 256 children and adolescents with NE, of whom 140 reached the clinical and laboratory evaluation phase. The structured protocol evaluation of these 140 participants resulted in the following diagnoses: NE complicated by urinary disorder and/or urinary infection (27 participants), hypercalciuria (4 participants), nephropathy (3 participants) and ADHD (1 participant). Of the remaining 105 participants who reached the clinical and laboratory evaluation phase, 17 failed to complete the study protocol, and 88 were scheduled for PSG. Of these latter 88 participants, one went into remission before the procedure; among the remaining 87 participants who did undergo PSG, six were diagnosed with severe apnea and sent for specialized follow-up.

The initial clinical findings of 82 MNE participants were evaluated, including the participant who went into remission. Among these 82 children adolescents, 62 were male (75.6 %), the mean age was 9.5 ±2.6 years and 72 (85.2 %) presented with primary enuresis. Thirty-four had attempted some type of previous treatment for NE, and five patients had undergone more than one type of therapy. Thirteen patients (15.9 %) had attempted alternative therapies (psychotherapy, color therapy, homeopathy, acupuncture, etc.).

The socioeconomic survey of the families of patients with MNE showed that 59/81 (72.8 %) patients belonged to higher economic status categories (A, B).

Clinical evaluation

Anamnesis

Among the 82 patients evaluated, 65 (79.2 %) reported frequent NE episodes, with an average of 5.9 (±1.93) nights/week, 57 (69.5 %) reported one to two bedwetting episodes per night and 80 (97.6 %) had a history of nocturnal polyuria. The use of diapers at night was reported by 81 (98.8 %) patients. Only 47 (57.3 %) parents were able to provide information on the number of times their child urinated during the day. Information regarding the period of the first NE episode was not available for 17 of the 82 patients (20 %); 38 (46.4 %) patients reported the first NE episode after the second hour of sleep onset. Fifty-four parents (of 74) admitted making routine attempts to awaken their child during the night with the aim to take him/her to the toilet to urinate, and 50/56 parents reported that their children slept so very deeply that they could not be awakened at night under any circumstances.

Toilet training was initiated by family decision in 50 of the 82 (61 %) patients and by school demand in 18 (22 %) patients. History of prematurity and of admission to neonatal intensive care with orotracheal intubation was reported for 14 (18.7 %) patients. Other reported medical conditions were: respiratory diseases (34 patients, 41.5 %), headache (5 patients, 5.1 %), previous history of urinary tract infection (>12 months before study entry) (11 patients, 13.4 %).

History of bedwetting was reported for at least one family member during childhood in 71/78 (91 %) patients. In 15 % of respondents, a family history of NE was reported by both parents.

Of the 82 patients, constipation and functional fecal incontinence were reported in 37 (45.1 %) and six (7.3 %), respectively. The age of bowel toilet training occurred between 24 to 36 months in 48/82 (58.5 %) patients, 56/82 (68.3 %) patients described Bristol ≤3 and 61/64 (95.3 %) were positive for Rome III criteria.

Clinical examination

All 82 participants presented normal findings in the clinical and neurologic examination. The body mass index Z score was within normal range in 44 (53.7 %) patients, 25 (30.5 %) patients presented with overweight, obesity was diagnosed in ten (12.2 %) patients and malnutrition was diagnosed in three (3.7 %) patients.

Table 1 summarizes the main findings of the medical history and clinical examination of the participants diagnosed with MNE.

Bladder and bowel diary

All participants completed a diary on urinary and bowel habits diary for 7 days and a diary on bedwetting frequency for 30 days. The information given by the parents in the initial interview regarding their children's micturition habits during the day was confirmed in most of the diaries. To the contrary, the number of "wet" nights initially reported by the parents greatly exceeded the number of events registered in the diary (p <0.00).

Sonography

Sonographic evaluation of the kidney and urinary tract demonstrated normal kidneys in all 82 patients. The mean bladder thickness was found to be 0.23 (±0.03) mm; bladder thickness was normal in 76 (92.7 %) patients and exceeded 3 mm in six (7.3 %) patients. The bladder capacity was normal in 55 (67.1 %) patients, and a small bladder capacity was

Table 1 Demographic and clinical parameters of 82 participants with monosymptomatic nocturnal enuresis

Data acquisition	Demographic and clinical variables	n (%)
Anamnesis	*Gender*	
	Male	62 (75.6 %)
	Female	20 (24.4 %)
	Type of MNE	
	Primary	72 (85.2 %)
	Secondary	10 (12.2 %)
	Number of events/week	
	Frequent (≥4 times)	65 (79.2 %)
	Number of events/night	
	Up to 2 events/night	57 (69.5 %)
	Previous NE treatment	
	Yes	34 (41.4 %)
	Past medical history	
	Prematurity	14 (18.7 %)
	Respiratory diseases	34 (41.5 %)
	Urinary infection	11 (13.4 %)
	Heredity	
	History of NE in first and second-degree relatives	71 (91 %)
	Comorbidities	
	Constipation	37 (45.1 %)
	Functional fecal Incontinence	6 (7.3 %)
	Mild/moderate apnea	33 (37.9 %)
Clinical examination	Obesity and overweight	35 (42.6 %)

MNE, Monosymptomatic nocturnal enuresis; NE, enuresis

determined in 27 (32.9 %) patients. Comparison of measured values by sonography with micturition volumes reported in the bladder diary revealed significantly higher volumes in the voiding diary (p <0.02).

The evaluation of the transverse diameter of the rectum by pelvic sonography showed an average value of 28.6 ±0.77 mm; in 27 of the 82 (32.9 %) patients, the diameter of the rectum exceeded 30 mm.

Constipation and functional fecal incontinence

In 67 of the 82 (89.3 %) patients at least one of the adopted diagnostic criteria for constipation was positive. Constipation was treated with dietary orientation in all patients, but pharmacological treatment was necessary in 68 (82.9 %) patients, and 39/68 (57.4 %) patients were successfully managed with lactulose monotherapy.

Sleep diary and PSG

Snoring was diagnosed by the Sleep Disturbance Scale in Childhood in 31 of the 82 (37.8 %) patients; nine (11 %) patients had previously been submitted to adenotonsillectomy. Sleepwalking was reported in four (4.9 %) patients, nightmares in eight (9.9 %) patients and bruxism in 25 (30.9 %) patients. The scores on the Epworth Sleepiness Scale and the Questionnaire Berlin were normal for all the patients.

As previously described, PSG was performed in 87 of 88 patients with MNE. The apnea hypopnea index was considered to be normal in 48 (54.0 %) patients, mild (between 1 and 5 events per hour) in 30 (34.4 %) patients and moderate (5–10 events/h) in three (3.4 %) patients. Severe sleep apnea was confirmed in six of the 87 (6.9 %) participants who presented innocent findings during clinical evaluation. During PSG, nocturnal polyuria was confirmed by diaper weight in 21.3 % (17/82) of patients.

Physical therapy evaluation

As chronological age influences postural control, participants were divided into two age groups, Group A (between 6 and 11 years) and Group B (aged 12–16 years). Table 2 shows the descriptive analysis of the primary COP area in the four sensory conditions studied.

Table 2 Median center of pressure displacement area in the four sensory conditions by age group

Conditions	Age group[a]	Enuresis group[b]
Open eyes on a stable surface	A (51)	3.1 (1.68/4.49)
	B (31)	1.91 (1.44/3.49)
Closed eyes on a stable surface	A (51)	3.39 (2.04/6.36)
	B (31)	3.52 (1.54/4.0)
Open eyes on a unstable surface	A (51)	3.53 (3.07/8.63)
	B (31)	3.57(2.45/5.91)
Closed eyes on a unstable surface	A (51)	4.11 (3.07/8.63)
	B (31)	3.71 (2.45/5.91)

[a] Group A: participants aged between 6 and 11 years; Group B: participants aged between 12 and 16 years. The number of children and adolescents in each group is given in parenthesis

[b] Data are presented as the median with the interquartile range (Q1–Q3) given in parenthesis

Table 3 Comparative distribution of quality of life scores (PedsQL 4.0), in the four dominions, according to the opinion of 65 patients with MNE and their parents

PedsQL 4.0	Parents (SD)	Children (SD)	p
Physical	90.18 ± 17.89	77.31 ± 16.20	0.00
Emotional	70.87 ± 21.03	65.52 ± 20.81	0.08
Social	87.71 ± 18.78	80.84 ± 19.84	0.04
School	74.06 ± 25.54	72.39 ± 19.60	0.69
Total score	80.71 ± 14.61	74.01 ± 14.41	0.00

Data are presented as the average ± standard deviation

PedsQL 4.0: Pediatric Quality of Life Inventory version 4.0; SD: standard deviation

Psychological assessment

Of the 82 participants, 77 (93.9 %) completed the CBCL response analysis. The participants' average scores remained below 60. The overall problem index averaged 58.2, with a median of 61, showing that, in general, participants were at the borderline range for behavioral problems. The index of externalizing problems, considered the most important causal factor for the treatment of enuresis, was on average 53.7 (±12.9), indicating a low frequency of this problem. The index of internalizing disorders was on average 58.2 (±11.6), with a median of 61, which is below the clinical range.

One participant presented characteristic behavioral changes compatible with ADHD during the initial clinic visit. This diagnosis was confirmed after further specialized evaluation.

The results of the PedsQL 4.0 questionnaire were analyzed in 65 of the 82 (79.3 %) patients. The responses of the children and parents/guardians are shown in Table 3.

Discussion

This study evaluated, in a cohort of patients with MNE, factors traditionally described in the literature as associated with NE [27–33], but not routinely assessed by a structured multidisciplinary protocol. Our results confirm that patients with NE may present multiple chronic clinical conditions and comorbidities. The prevalence rate of NE reported in epidemiological studies which have compared MNE and NMNE patients as groups, ranges from 6 to 28.6 % [32]. Most of these studies were developed before ICCS nomenclature standardization in 2006 [1].

In our study, MNE was characterized on the basis of structured anamnesis, complete physical examination, bladder and bowel diary evaluation and complementary work-up. Using this protocol, we were able to detect a significant proportion of participants who presented a chronic clinical condition that required specific care and who would therefore not benefit from inclusion in an MNE treatment protocol. The reported prevalence of constipation in the Brazilian pediatric population ranges from 14.7 to 38.5 % [34]. We were able to demonstrate constipation to be highly prevalent in our cohort, as already described in the literature [9, 28, 34]. As the diagnosis of constipation is still in need of a gold standard, we have included as instruments of evaluation, the Rome III criteria, a bowel diary, Bristol scale and measurement of the rectum diameter by sonography. Pharmacological treatment was necessary in 68 of the 82 (82.9 %) patients. A close relationship of constipation with MNE and NMNE is well described in the literature [2, 9, 28], which underscores the need for its identification and resolution prior to the initiation of MNE therapy.

We found that in our cohort of children and adolescents with MNE, the condition predominates in males and is frequently an inherited trait. These findings are in accordance with previously reported results from epidemiological studies. MNE has been reported to present predominantly without nocturnal polyuria and urinary incontinence to have a tendency to occur multiple times per night and in more than four nights a week [28–31]. Our results do differ from previously reported ones with respect to the reported predominance of children and adolescents of higher sociocultural level with MNE [29–31, 33]. It is possible that the media routes we selected to publicize the study did not reach the less economically privileged segments of the community. On the other hand, it may not be possible to extrapolate the results of the evaluation instrument that was used in our study, which was developed to evaluate the purchasing power of the Brazilian family unit, to those of international studies.

Based on universal parental experience, sleep in children with NE is deeper than that in non-enuretic ones [35]. The

analysis of sleep in enuretic patients by neurophysiological variables, using EEG and PSG studies, has produced conflicting results. Some studies have found EEG signs of deeper sleep, based on an increased delta component during the night (N3 sleep percentage), while others have shown the sleep of enuretic patients to be more superficial [36] when compared with normal controls; in addition, there are studies in which no difference was demonstrated between the sleep of enuretic children sleep and either normative data [10, 37] or the sleep of a control group [38]. Our study participants presented with a normal sleep pattern, confirming the latter studies' results.

In a recent literature review, the prevalence of childhood obstructive sleep apnea syndrome ranged from 0 to 5.7 % [39]. Our study's participants presented a high prevalence of mild to severe sleep apnea (39/87; 46 %). The correlation between sleep enuresis (SE) and sleep disordered breathing (SDB) in both adults and children [40, 41] is supported by the improvement or full resolution of SE after treatment of SDB by adenotonsillectomy or intranasal corticosteroids [41, 42] and by community studies showing that children with habitual snoring had primary NE more often than those without snoring [43]. Therapy-resistant enuretic children were recently found to have subclinical signs of disordered breathing reflected by a high frequency of hypopneas, while the standard polysomnographic variables were normal [44]. Accordingly, another study showed that SE was significantly associated with presence of moderate-to-severe obstructive sleep apnea after adjustment for tonsillar hypertrophy, obesity, gender and age [45].

Recent studies have shown sleep fragmentation due to increased periodic leg movements during sleep in children with NE [46]. These studies however, included refractory NE from a tertiary care center and did not exclude children with ADHD or restless leg syndrome [46, 47]. In our study, we excluded any participant with a neurological and psychiatric condition that could be linked to increased movement during sleep. The participants in our study did not manifest periodic leg movements, but this alteration should be systematically evaluated in future studies.

The CBCL scores of our participants confirm the results of other published studies showing borderline range values for behavioral problems in all evaluated areas [6, 16, 48]. Our findings also demonstrate that patients with MNE present lower quality of life global ratings, especially in the physical and psychosocial spheres, as also shown in recent studies of NE [49, 50]. It is noteworthy that, in the present study, quality of life evaluation scores, as expressed by the participants, were significantly lower than the scores of their respective parents for the same questions, pointing out that parents may underestimate the quality of life compromise of their children. Moreover, the discrepancy between the intensity of the enuretic phenomena as per parents' evaluation, during the structured anamnesis, and the NE frequency reported in the bladder diary may reflect the heavy burden NE poses to the family routine. The perception of a disrupted family routine due to NE may add to the reasons for the worse quality of life scores as per patients' opinion. Treatment success most probably depends on direct emotional support of the child/adolescent by the clinical team.

There are no established normative values of balance for children and adolescents reported in the literature; neurological development promotes natural changes in these aspects, with the amplitude of body oscillations decreasing with age and muscular responses becoming more organized in the face of sudden disruptions with posture alignment and stability [12]. Our assessment of balance allowed us to identify delayed motor performance for age, with associated losses in motor skills suggesting motor cortex maturation deficit. The motor cortex includes areas of voluntary urination control, as well as areas for the planning and execution of fine movements. Any deficit in the maturation of these cortical areas can interfere directly with postural control, as the latter emerges from the dynamic interaction between the skeletal muscle, neural and sensory systems and involves control of the body's position in space to maintain stability and guidance.

In conclusion, considering the multiple clinical conditions associated with NE, including the need to differentiate MNE and NMNE [51], the results of our study show that a full assessment of the NE patient is not only important but that it needs to be based on a structured protocol, with multidisciplinary assessment. Our data suggest that anamnesis, physical examination and elimination diaries need to be complemented minimally with a urine sample for conducting urinalysis and determining a urinary calcium/creatinine ratio and with a urinary sonography evaluation. This set of tools are useful to differentiate NMNE from MNE and serve as a guide for better therapeutic planning [1, 2, 50]. Our assessment of balance confirmed previous findings indicating that the MNE is associated with delayed motor performance for age, suggesting a motor cortex maturation deficit. This finding points out to research opportunities in elucidating NE pathogenesis, it may also possibly affect MNE treatment prognosis. Our data confirm that MNE may lead to poorer quality of life scores which may not be fully perceived by the patient's caregivers, suggesting the need for a more individualized clinical follow-up of patients and their families.

The cohort of patients with MNE identified in our study will be part of a randomized trial of MNE. We suggest that the therapeutic response of the present cohort to different MNE treatment modalities may be optimized as, unlike cohorts from most of the available studies, it is constituted exclusively of monosymptomatic patients with therapeutically managed comorbidities.

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