REVIEW ARTICLE

Monosymptomatic nocturnal enuresis

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Abstract

Objectives: monosymptomatic nocturnal enuresis (MNE) plays a very important role in the practice of pediatrics due to its high prevalence, its psychosocial impact, and its controversial etiology and treatment. Our objective was to show that MNE can be a well-defined clinical entity (monosymptomatic), but it can also be a symptom of urinary disorder, thus requiring a completely different therapeutic approach.

Methods: the literature presents numerous publications related to the matter of MNE, thus we tried to select, for this review, the classical and the most recent publications from internationally recognized authors; in addition, we also have a 13-year work experience at the Unit for Urinary Disorders of the Pediatric Nephrology Center of the state of Paraná (Unidade de Distúrbios Miccionais - Centro de Nefrologia Pediatrica do Paraná).

Results: the lack of a well-defined, international consensus on the concept, terminology, and classification of MNE is an obstacle for the assessment of the numerous studies found in the literature. The individualization of the MNE clinical entity is the fundamental starting point for providing appropriate guidance for patients. Enuresis can be found in most societies and, thus, it gives way to several interpretations and forms of treatment. There is a consensus, however, on the damage to the self-esteem of enuretic children, and consequently, on the advantage of proper treatment.

Conclusions: in most cases, MNE is kept as a family secret while children remain without proper guidance and treatment and suffering with the lack of understanding and damage to their self-esteem. Doctors should survey patients extensively for MNE during pediatric appointments. It is possible to discard other diagnoses with a detailed survey of habits, quality of the urination, and history of urinary infection and a meticulous physical examination. MNE should be faced as a medical problem worthy of the attention of professionals and patients' families.


The history of nocturnal enuresis

Ebers papyrus, the first document to address enuresis, found in Luxor 3,500 years ago, revealed that mothers and children used to take medicines made from water plants, suggesting that enuresis had a familial nature. Thirty-five centuries afterwards, Guyon brought up the family incidence of enuresis. At the time of Greek Romans, Aristotle, a follower of Plato, was the first to reflect upon the causes of enuresis by observing children’s difficulty in waking up from sleep. In the Byzantine civilization, enuresis was associated with bladder neck relaxation, and in that case, tonic beverages such as hot wine or oil were recommended; during the Middle Ages, Saint Catherine of Alexandria (whose memorial day is November 25) became known for curing enuretic people. During the Renaissance, Paulus Begellardus drew up the first treaty on pediatric medicine which, in its 20th chapter, affirmed that “parents get particularly irritated when their children wet the bed regularly, sometimes way into the pubertal stage...”. In 1544, Thomas Phaer, the father of Pediatrics in England,
recommended several therapies that consisted of powdered rooster windpipe, bladder from animals, intestine and brain from mice, in the chapter “Bedwetting” of his work Boke of Chyldren. Such therapies based on animal organs persisted for several centuries.

In modern times - starting in the 17th century - the first anatomical studies were performed. The book Practica Medicinae refers to enuresis as “a cold and damp mood alteration”, recommending the use of astringents in the suprapubic region. In the book Partes Duae De Morbis Puerorum, the author almost admits that enuresis is caused by demons and witchcraft.

Thomas Dickson, in the 18th century, was the first to report the efficiency of suckers in the sacral regions of enuretic children, considering that most nerves leading to the bladder pass through the sacral foramen.

The knowledge about physiology started to develop in the 19th century, and clinical observations became similar in the whole literature. Guersent (1815) described the hereditary factor, higher incidence among boys and in economically-underprivileged social classes, and the effect of enuresis on children’s mind, by referring to enuresis as “an aspect of sadness and shame that also affected their intelligence”. The bladder was considered to be the determinant factor for enuresis due to the weakness, irritability, and lack of sensitivity attributed to it. This conception originated two forms of treatment: one for stimulating and another for slowing down bladder activity. The stimulation of bladder activity was carried out by the intravesical instillation of several substances or through cold showers in the pubic and perineal region, sea bathing, or use of aromatics.

In the late 19th century, galvanic or faradic current discharges used to be gently applied on the entire genital region of enuretic children. Technical reports on this technique became available all over the world, and Hernamann-Johnson, in the early 20th century, said that “the simplest method consists in introducing a metallic plug into the bladder and discharge the electric current up to the children’s limit of tolerance”. Trouseau and his followers preached the use of soothing therapy, especially one that was based on the belladonna, a plant that became very popular during a long time. Other hypotheses such as small-sized bladder, defective bladder neck, defective trigone and urethral meatus with reduced sensitivity led to new treatment options such as bladder distension with fluids, insufflated vaginal rings in order to constrict the bladder neck, catherization with silver nitrate to sensitize the urethra, and bedwetting aids that kept a 45 angle between trunk and hips.

Guersent was the first to describe relative nocturnal polyuria; only hundreds of years after that, Poulton and Hinden brought this hypothesis to light again, which did not arouse any interest until 1980, when researchers found out that enuretic children produced less antidiuretic hormone (ADH) during the night.

Scolding and punitive attitudes that attacked children’s self-esteem were recommended for “simulators”, and urethral occlusive devices such as the one invented by Wilks, which consisted of a velvet-covered iron tube shaped like a boy’s penis, or that created by Labat, which had the advantage of leaving circulation free within the cavernous bodies, were used.1

In the 20th century, three events remarkably changed the history of enuresis: alarm therapy, imipramine and desmopressin.

Development of vesicourethral sphincter control

Soon after birth, urination occurs spontaneously as a medullary reflex. From the first year of life onwards, two important events take place: increase in bladder capacity and neural maturation of frontal and parietal lobes. The cortical command produces the sensation of bladder filling; however, neurological maturity to initiate or inhibit urination is not present yet. The complete maturity with voluntary control of external vesicourethral sphincter and ability of cerebral cortex to initiate or inhibit detrusor contraction occurs only later. This allows children to control urinatio and defecation, adjusting them according to socially defined patterns.

At the age of five, 85% of children have total vesicourethral control, while the remaining 15% become continent at an annual rate of 15%. At the pubertal stage, 2 to 5% continue to be enuretic, and in adulthood, this rate is approximately 1.5 to 3%.2

Definitions

The word enuresis originated from Greek and means “wet oneself”. Therefore, it defines socially unacceptable urinating behavior.

Nocturnal enuresis means urinating during sleep. This episode occurs at least once a month.3

Since it is a unique symptom after the habitual age at which children learn to control urination, enuresis is considered monosymptomatic, and presupposes normal functioning of the nervous and urinary systems or absence of other well-defined organic conditions as causative agent. If nocturnal enuresis is associated with other symptoms, it is considered polysymptomatic.4

A recent international agreement suggests classifying monosymptomatic nocturnal enuresis (MNE) as primary, secondary, familial or polyuric. Primary enuresis refers to inability to maintain urinary control from infancy; secondary enuresis is a relapse after control (at least 6 months) has been achieved; familial enuresis is when at least one parent has a previous history of enuresis; and polyuric enuresis is when the nocturnal urine volume exceeds functional capacity.3

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Epidemiology

The accuracy of data on the prevalence of MNE is currently hampered by the lack of standardized criteria for the selection of patients, in addition to the influence of geographic, social and cultural factors. The literature presents an MNE prevalence rate of 3 to 22% at the age of seven, and 0.4 to 8.4% at the age of ten. Usually, this rate remains around 10% at the age of seven. MNE is more frequent in boys up to the age of ten years who belong to lower social classes; the incidence of MNE is incontestably influenced by genetic factors. After the age of ten, the frequency is the same for both boys and girls.

Pathogenic factors

MNE is characterized by three evident situations: nocturnal urinary urgency, absence of enuresis alarm, and significant higher incidence among children whose parents used to be enuretic or have nocturia.

Based on this evidence, the participation of several factors has been investigated, including bladder capacity, uninhibited detrusor contractions exclusively during sleep, volume of nocturnal diuresis, ability to wake from sleep, and the presence of enuresis at different sleep stages.

These investigations prompted classifications that may consistently guide the adoption of appropriate therapies. One of these classifications groups MNE into types I and II if it is secondary to a waking disorder, and type IIIb if it is secondary to a nocturnal bladder dysfunction. A recent classification based on possible etiological factors, considering an abnormality in the circadian rhythm of vasopressin, groups nocturnal enuresis into polyuric, familial, primary and secondary.

1) Genetic factors

MNE is a development disorder whose hereditary component has a heterogeneous character, described since 1890, which involves parents, brothers and sisters and other close relatives, and increases the probability of enuresis by 2 to 6 times. Children whose mother and father have previous history of enuresis present 77% of chances to suffer from this disorder, and if only one parent used to be enuretic, the chances amount to 44%; however, if there is no previous parental history of enuresis, the chances drop to 15%.

Children who were brought up in a kibbutz, away from their parents, have the same hereditary influence. The probability of identical twins having enuresis is 68%, while in nonidentical twins the probability is 36%. Molecular biology seems to have a better explanation to the genetic transmission of enuresis. Genes found on chromosomes 12q, 13q and 8q seem to be involved.

2) Delay of the circadian rhythm of antidiuretic hormone (ADH)

The amount of ADH in the bloodstream, secreted by the posterior pituitary gland, is reduced soon after birth and, after one year, ADH levels equal those presented by adults. ADH levels usually increase during the night, resulting in reduced urine volume. A disorder in the circadian rhythm of ADH causes increased urine production, exceeding bladder capacity and explaining enuresis, although it does not explain why children do not wake up from sleep when the bladder is full.

The mechanisms of circadian rhythm regulation of hydroelectrolytic balance have not been clearly understood yet. Nyctohemeral variations in central volemia and intrathoracic volume receptors influence the production of ADH and urine. This circadian rhythm is not present at birth, and undergoes a maturation process during the first childhood. A defect or delay in the maturation of the regulating system may give rise to relative nocturnal polyuria. The identification of genetic markers can optimize the use of desmopressin. The response to desmopressin does not prove this theory, as diuresis is reduced even in children with normal ADH levels. There is a correlation of nocturnal polyuria with low ADH levels and low urine osmolality or significant difference in ADH levels after six months of desmopressin therapy.

Some parameters such as urine osmolality, bladder capacity, diurnal and nocturnal diuresis volume, involvement of urinary prostaglandins in water excretion control, antagonizing the osmotic effect of ADH in the renal medulla, and levels of aquaporins (proteins that participate in water transportation), have been analyzed in order to predict the response or nonresponse to desmopressin therapy.

3) Sleep and wakefulness

There has been an attempt to define the correlation of enuresis with different sleep stages; however, results have been inconclusive. Parents usually report that their enuretic children have deep sleep, showing a tendency towards wakening difficulty or inability to recognize the sensation of bladder filling during sleep. The reason for this wakening dysfunction may be related to immature thalamic function.

Even though there is some difference in terms of wakening patterns in enuretic children, their sleep has presented better quality than that of nonenuretic children; Furthermore, enuretic children seldom have sleep disorders such as nightmares, insomnia, agitation, sleepwalking or bruxism.

4) Bladder capacity and uninhibited detrusor contractions

Small bladder capacity has been described as an MNE etiologic agent. The limited number of urodynamic studies
in enuretic children and the nonstandardized selection of patients cast doubt on the interpretation of results.\textsuperscript{2,3,15} No significant difference has been effectively determined so far.\textsuperscript{30}

If there is more than one enuretic event on the same night and higher frequency of diurnal urination, or in cases that are refractory to all forms of treatment, it is necessary to rule out possible bladder instability through the urodynamic study. These children benefit from an anticholinergic treatment.\textsuperscript{2,3} The definition of MNE presupposes normal vesicourethral sphincter function.\textsuperscript{30} Uninhibited detrusor contractions that are only present during sleep have been described and may express residual immaturity.\textsuperscript{30}

5) Psychological implications and nervous system

The idea that enuresis is a symptom of emotional stress has been replaced with the evidence that most enuretic children manifest secondary psychological disorders that affect their self-esteem; these children profit from early guidance and treatment.\textsuperscript{31-34}

Organizations such as ERIC (Enuresis Resource and Information Center), in England,\textsuperscript{35} or Brazilian groups of researchers have jointly worked with professionals and in society in order to advertise, clarify and research about the topic, in addition to encouraging early treatment or reducing

6) Other factors

Intestinal constipation acts as a mechanical factor, preventing the bladder to expand to its full capacity. Other factors may correlate with enuresis, such as allergy to cow’s milk, effects of caffeine or cocoa derivatives, airway obstruction (sleep apnea) or even nocturnal fluid overload (induced enuresis).\textsuperscript{15,23,30}

Several diurnal urinating behavior alterations have been interpreted by family members as distraction or voluntary acts that could be controlled by children, and many times are not spontaneously reported. The presence of these signs deserves investigation and differentiated treatment.

2) Physical examination

Some alterations that require differentiated diagnosis in relation to other urological events are:\textsuperscript{4} urine spots and fecal residues on underwear; vulvovaginitis, meatalitis, perivulvar dermatitis, synchiae of the lips, epispadias or hypospadias; reflex alterations in lower limbs or other neurological signs; nevus or abnormal pigmentation of the fossa.

3) Additional exams

Qualitative urinalysis and urine culture are necessary in order to rule out the presence of leukocyturia, bacteriuria, hematuria, proteinuria, glycosuria, oliguria and bacteriuria.

Urinary tract echography is useful in cases in which anamnesis is not elucidative. The echography provides interesting information on the structure of the bladder wall, renal parenchyma, and urinary pathways or even on bladder capacity and the presence of occasional posturination residues. This examination may suggest the presence of functional or structural disorders of the urinary tract and, in these cases, if MNE is ruled out, voiding cystourethrography and/or urodynamic investigation are recommended.

Treatment

1) Treatment onset

Considering that MNE is a benign condition, its spontaneous resolution rate is approximately 15\% per year, the placebo effect is high, and that there is a possibility of relapse after successful treatment, treatment regimens that are free from side effects are preferred. However, the effects on enuretic children’s self-esteem is a good indicative sign that the matter deserves serious consideration.

The ideal age for treatment onset depends on each patient’s individual condition, their maturation, and the level of family tolerance. General guidance may start before the age of 5, and drug or nondrug treatment may be implemented after the sixth year of life.

2) Interfering factors

The identification of some factors may help to select the types of treatment, which include sound or vibratory alarm, psychological support, or prediction of desmopressin response. The following factors may interfere with therapeutic results: children’s and family’s actual motivation; the difficulty children have in waking up or ability to wake
to an alarm or call; presence of encopresis or intestinal constipation; presence of night terror, dyslexia, school-related disorders, rejection, aggressiveness or passiveness, low self-esteem and family hardships; reduced bladder capacity or greater volume of nocturnal diuresis compared to diurnal diuresis; impact of enuresis on family environment; socioeconomic status of the patient.

3) Interpretation of therapeutic results
There has been an attempt to standardize the interpretation of therapeutic results, thus allowing comparative studies. A cure or total response to treatment is equivalent to a reduction of enuretic episodes in at least 90% of nights. Improvement or partial response corresponds to a reduction of more than 50%. In some cases, enuresis turns into nocturia.3,38

4) General Guidelines
Some preliminary guidelines and nonspecific actions should also be considered for children younger than 5 years old10,39-41, discontinuation of diapers; maintenance of urinating schedules; bladder voiding before going to bed; perception of bladder filling; awareness of the ability to control the sphincter either to initiate or stop urination. Among the major measures, we have: show children that MNE is very frequent and several schoolmates suffer from the same problem; try to remove guilt and motivate children; avoid excessive fluid intake at night, eradicate any punitive attitudes, and provide positive support instead.

5) Alarm therapy
The first described device dates back to 1904, when a German physician designed a hospital mattress with a mechanism that indicated when nurses had to change the clothes of hospitalized children; some of the children did not wet the bed anymore after spending some time in that hospital.1,42

The therapy yielded good results, approximately 70 to 90% on the medium and long run, with a reduction in the incidence of relapses between 0 and 30%; was also safe and simple to apply, and did not present side effects. In spite of this, alarm therapy has been scarcely used in Brazil. The major reasons for this include lack of immediate results, cultural aspects, unavailability, form of commercialization, and lack of expertise.

The principle of alarm therapy is based upon the electrical conduction of urine. Every time involuntary urination occurs, a sound or vibratory mechanism is triggered, waking children up and having them cease urination. Children may not wake up immediately or just wake up during or after urination, gradually learning to anticipate or perceive urinary urge. Expected results are only achieved after at least 4 months of continued use.

This method depends a lot on motivation, that is, patients who will not mind waking up. Alarm therapy can only be used on children who are able to understand and control the device.

Before choosing between the sound or vibratory model, it is important to know which modality is fit for the child. The vibratory model offers the advantage of not waking up other family members. In Brazil, we do not have any enuresis alarms available on the market. In practice, a handcrafted device is used, yielding good results.

Some causes of treatment failure include unmotivation, early discontinuation, difficulty in waking up, night terror (children wake up and cannot sleep any longer), behavioral disorders, inadequate home environment, mother’s anxiety, more than one nocturnal episode, low socioeconomic status. The reasons for discontinuation are family history, mother’s intolerance, children’s low self-esteem, and behavioral disorder.

When results are satisfactory, some authors suggest increasing fluid intake before discontinuing alarm therapy.

If cure or total recovery fails, a combination of alarm therapy and desmopressin should be used. This combination allows faster results, providing the family with the opportunity to get acquainted with the alarm device, thus warranting more definitive results.10,44 The combination of alarm therapy and desmopressin is recommended for at least 6 months; after that, only alarm therapy should be used until totally satisfactory results are obtained. This regimen is recommended especially for older children who were refractory to different forms of treatment. A 6-month combination therapy may result in 57% of cure, 21% of partial response, in addition to being safe and free from side effects.45

Imipramine may be used, depending on the patient’s social status.

6) Drug treatment
a) Desmopressin acetate (DDAVP)

Desmopressin is structurally analogous to the antidiuretic hormone, which reduces the nocturnal production of urine. The 1-deamino-8-D-arginine-vasopressin molecule was synthesized in 1966. The deamination of N-terminal half-cysteine in position 1 causes an increase in antidiuretic activity and duration of action (10-12 hours) due to a higher action on V2 receptors of collecting duct cells. The replacement of L-arginine at position 8 with D-arginine is responsible for the reduction in the vasopressin activity, causing the action on V1 receptors of smooth muscle fibers to be almost nonexistent.

The efficiency and safe use of desmopressin in MNE has been described for over 10 years. Several literature reports show approximately 70% of total and/or partial response.2,20,39,48-50
The optimization of desmopressin use is based on parameters such as normal bladder capacity, patient’s age, increased volume of nocturnal diuresis, and urinary osmolarity. The selection of cases, whose pathogenic mechanism involved is relative insufficiency of nocturnal ADH secretion, may provide higher efficiency.

Desmopressin is available in nasal and oral solutions. Nasal desmopressin is the most widely used. Oral desmopressin is recommended for children with rhinitis or respiratory tract infections. Dosage equivalence for the nasal solution is 20 mg, and 200 mg, for the oral solution. The dosage may be reduced in 50% or doubled after 2 weeks, depending on the initial response, and maintained for 3-4 months, with later gradual reduction. The antidiuretic effect starts 15 to 30 minutes after administration, reaching maximum effect between 2-3 and 10-12 hours. Oral desmopressin has lower bioavailability, its maximum concentration in 40-70 minutes, with a maximum concentration obtained within one hour.

Desmopressin must be administered 1 hour before bedtime, and it is necessary that fluid intake be limited to 30 ml/kg, 2 hours before to up to 12 hours after administration so that the risk for hyponatremia and even seizures secondary to water intoxication can be avoided.

Excellent tolerance and harmlessness have been widely observed. Some possible side effects are mild headache (2%), nasal congestion, rhinitis and epistaxis (1%), and abdominal pain (1%). Desmopressin must not be prescribed to children with polydipsia, high blood pressure, or heart disease.

b) Imipramine

This tricyclic antidepressant has been banned from medical prescriptions due to potentially lethal intoxication risk, which are unjustifiable if we consider the benign nature of enuresis. Imipramine has gained widespread use since 1960, although its action mechanism is not clear, and is probably related to anticholinergic and sympathomimetic effects. The antidepressant effect does not seem to be involved, since other antidepressants show no effect on enuresis. Despite the toxicity potential of imipramine, it is still a therapeutic option in Brazil, especially for preadolescents, since alarm therapy and desmopressin depend on more favorable social conditions.

The therapeutic result is nearly similar to that of desmopressin, also in terms of relapse episodes. The dosage ranges between 0.5 and 2.0 mg/kg/day, not exceeding 50 mg/day up to the age of 12 years and 75 mg/day after this age. Imipramine is administered in a single dose, approximately 2 hours before bedtime, and yields the desired results, that is, a reduction of over 50% in enuresis frequency. After 2 weeks, the dosage may be readjusted or maintained for 3 to 6 months, and then gradually reduced until discontinuation is possible.

c) Anticholinergics

It is important to emphasize that there is no recommended use of anticholinergics for MNE. If bladder instability is confirmed through urodynamic investigation, we classify enuresis as a symptom of urination disorder, and a specific treatment protocol, including the use of anticholinergics, is recommended.

7) Use of alternative medicine

The practices of herbal medicine by means of infusions; aromatherapy through essential oils such as cypress, known for its antispasmodic and rebalancing properties; oligotherapy through the combinations of manganese-zinc, zinc-copper or fluorine, known for their tonic effect on the sphincter; and naturopathy-iridology, which contemplates enuresis within a global context involving the digestive tract and energy consumption, have attempted to show efficacy; however, studies with more appropriate methodologies are still necessary.

Homeopathy associates a symptomatic, active medication (kreosotum or causticum) with early-night enuresis, and plantago major or chloralum with late-night enuresis. The background treatment takes the morphology and temperament of patients into consideration: calcarea carbonica for obesity-prone and slow children; calcarea phosphoricum for irritable and underweight children; or sepia for children who are very sensitive to cold; gelsemium sempervirens when children suffer from sleeplessness; and chamomilla sempervirens when sleep is agitated.

Crenotherapy also offers some treatment options. Results obtained through the Lons-le-Saunier Center in France, with 5,000 children treated between 1988 and 1992, were 23% of cure, 68% of improvement, and 9% with no results.

Hypnosis has also been used, and several retrospective studies were performed, with variable results (44-93%). Although results have been satisfactory, hypnosis has been seldom recommended.

Chiropractics, which consists of manipulation of the spinal framework, yields results similar to those of placebo. Acupuncture, traditionally used by the Chinese to treat enuresis, has also yielded good results. Foot acupuncture has also been referred, with 82% of cure, and 16% of improvement one year after treatment completion.
Conclusion

Although MNE has been reported since the times of Ebers papyrus (c.1550 AC), it is a present concern to children, their families and doctors. No treatment has proved to be universally efficient to all patients.

The wide variety of therapeutic regimens reveals the different theories on MNE pathogenesis. While these theories are still under discussion, the major factors that contribute to successful therapy are family support, children’s motivation, everyone’s patience, and especially an accurate and differentiated diagnosis, which personalizes MNE treatment.

References


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