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EDUCATIONAL ARTICLE

Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: A standardization document from the International Children's Continence Society

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Abstract *Purpose:* This document represents the consensus guidelines recommended by the ICCS on how to evaluate and treat children with nonmonosymptomatic nocturnal enuresis (NMNE). The document is intended to be clinically useful in primary, secondary and tertiary care.
Materials and methods: Discussions were held by the board of the ICCS and a committee was appointed to draft this document. The document was then made available to the members of the society on the web site. The comments were vetted and amendments were made as necessary to the document.
Results: The main scope of the document is the treatment of NMNE with drugs other than desmopressin-based therapy. Guidelines on the assessment, and nonpharmacologic and pharmacologic management of children with NMNE are presented.
Conclusions: The text should be regarded as an expert statement, not a formal systematic review of evidence-based medicine. It so happens that the evidence behind much of what we do in the care of enuretic children is quite weak. We do, however, intend to present what evidence there is, and to give preference to this rather than to experience-based medicine, whenever possible.

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Scope of the document

This document represents the guidelines recommended by the ICCS on how to evaluate and treat children with non-monosymptomatic nocturnal enuresis (NMNE). NMNE throughout the text will be taken to mean "enuresis in children with any other lower urinary tract symptoms and with a history of bladder dysfunction", in accordance with the updated ICCS terminology [1], which will be consistently adhered to. The document is intended to be clinically useful in primary, secondary and tertiary care. The text should be regarded as an expert statement, not a formal systematic review of evidence-based medicine. It so happens that the evidence behind much of what we do in the care of enuretic children is quite weak. We do, however, intend to present what evidence there is, and to give preference to this rather than to experience-based medicine, whenever possible. Furthermore, in cases where opinions differ widely between established experts in the field we have chosen to present both views rather than find a compromise. The reader can make an informed choice and future research will show who was right. The document was produced on the initiative of the ICCS Board and Standardization Subcommittee and according to fairly democratic procedures. Thus, the authors first completed a draft that was circulated among all ICCS members. Comments were invited and integrated into the text before it was finalized.

Background

It is well known that nocturnal enuresis is a common disorder among children. It has been documented that 15—30% of enuretic children can experience daytime incontinence [2—5]. It is likely that many more children suffer from subtle issues regarding bladder emptying, voiding postponement, and urgency and frequency than are actually documented in these publications. We are not going to address the role of polyuria in this monograph since it is well covered in the prior document on MNE published by the ICCS [6]. We will address the role of detrusor overactivity whether it is daytime and/or nocturnal. We will also discuss treatment strategies that are commonly used for overactive bladder and management of incomplete bladder emptying. There is increasing evidence that neuropsychiatric problems in children can be linked with daytime voiding issues and these same problems may play a role in nocturnal enuresis [7—11].

Definitions

Enuresis

Enuresis means wetting in discrete portions while asleep in a child who has passed his or her fifth birthday. The word nocturnal may be added for extra clarity, but it should be emphasized that the previous definition of enuresis denoting "an urodynamically normal, complete emptying of the bladder" [12] (Nørgaard et al., 1998) is no longer valid, since this would require ambulatory cystometric investigations before being able to use the correct terminology. Thus, bedwetting is properly called enuresis regardless of whether it occurs in a child with concomitant daytime incontinence or not, irrespective of suspected underlying pathogenetic mechanisms, and separate from results of cystometric evaluation of the same child. Enuresis just means wetting while asleep.

A child exhibiting incontinence during both day and night has two diagnoses: enuresis (or nocturnal enuresis) and daytime incontinence. The confusing term "daytime enuresis" is obsolete, and the term "nocturnal incontinence" — previously denoting bedwetting episodes that were presumed not to be due to normal complete emptying of the bladder — should now either be avoided or taken as being completely synonymous to enuresis.

Urinary incontinence

Incontinence means any involuntary loss of urine at a socially unacceptable place and time by a child aged 5 years or older whose general mental and neurological development indicates that bladder control should have been achieved. We often talk about *daytime incontinence* to distinguish it from nocturnal enuresis. In this document it should be clear from the context that the word incontinence is usually used to denote daytime incontinence. Of these, most cases can be considered to be functional forms of urinary incontinence. Organic urinary incontinence is extremely rare and can be due anatomic or neurogenic causes.

Fecal incontinence

Fecal incontinence is defined as voluntary and involuntary passage of feces in improper places and inappropriate times, from age 4 years onwards only after organic causes have been ruled out. Synonymously, the term 'functional fecal incontinence' can be used. The two main subtypes are those with and without any accompanying constipation. According to the Rome-III classification, two subtypes of fecal incontinence can be distinguished [13]:

- functional constipation
- nonretentive fecal incontinence.

Prevalence

Enuresis is a common problem among children and adolescents. If a wetting frequency of more than one "wet night" per month is taken into account, the prevalence of nocturnal enuresis is above 10% among 6 year olds [14], around 5% among 10 year olds [15,16], and 0.5—1% among teenagers and young adults [17]. The only epidemiological study analyzing children with NMNE is the British Alspac Study. Of 8242 7½-year-old children, 15.5% wet the bed in total and 2.6% had a frequency of 2 or more wet nights per week [18]. Of those children with frequent NE (2 or more wet nights per week), 68.5% were classified as monosymptomatic and 31.5% as 'polysymptomatic' [19].

Etiology

According to the ICCS definitions, NMNE consists of two different disorders: nocturnal enuresis and lower urinary tract dysfunction (LUTD) identical to those with daytime urinary incontinence (except daytime wetting does not occur). The main etiological factors in NE are: (1) polyuria, (2) an arousal disturbance during sleep and (3) lack of inhibition of the micturition reflex. These developmental disturbances are genetically based and can be modulated by environmental factors [20]. The etiological factors of LUTD are heterogeneous, based on the symptoms present (urge, voiding postponement, dysfunctional voiding, etc.).

Comorbidity

Comorbidity is defined as the co-existence of two or more disorders at the same time or sequentially. Children with elimination disorders have increased rates of comorbid behavioral or psychological disorders according to standardized classification systems such as the ICD-10 and the DSM-IV. Of possible combined bowel and bladder dysfunction, children with fecal incontinence (formerly encopresis) have the highest rates of comorbid behavioral disorders: 30—50% of all children have clinically relevant behavioral disturbances [20,21]. In total, approximately 20—40% of children with daytime urinary incontinence are affected by comorbid behavioral disorders [20,21]. In a large epidemiological study of a cohort of 8213 children aged 7½ to 9 years, children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety (11.4%), attention deficit (24.8%), oppositional behavior (10.9%) and conduct problems (11.8%) [22]. By the same group, 10,000 children aged 4—9 years were analyzed. Delayed development, difficult temperament and maternal depression/anxiety were associated with daytime wetting and soiling [23].

Of all types of functional elimination disorders, children with nocturnal enuresis have the lowest prevalence of comorbid disorders (20—30%) but this incidence is still significantly increased compared to non-wetting controls. Also, subtypes of nocturnal enuresis differ regarding comorbidity rates. A thorough discussion of other comorbid neuropsychiatric states associated with enuresis and daytime incontinence can be found in a publication document put out by von Gontard [7].

Evaluation

Evaluation of the child with NMNE should follow the guidelines outlined in the documents prepared in for the treatment of monosymptomatic nocturnal enuresis and functional bladder problems [6,24].

The first step in any diagnostic and therapeutic process is to create a good relationship with both the child and his/her parent(s). One should inquire and talk about all relevant facts and signs and symptoms openly.

Treatment

In NMNE, it is advisable to follow a sequence of steps.

1. Treat any constipation (or fecal incontinence) first, as effective treatment of bowel problems can lead to spontaneous remission of daytime incontinence [25,26].
2. Treat the underlying LUTD symptoms first, as effective treatment of an overactive bladder (or postponement, dysfunctional voiding) can lead to cessation of nocturnal enuresis.
3. If comorbid behavioral disorders are present, these often require specific additional treatments (such as stimulants and behavioral therapy in comorbid ADHD).
4. If nocturnal enuresis persists, then standard treatment for monosymptomatic nocturnal enuresis can follow (alarm treatment, desmopressin). A full discussion of this management can be found in the most recent document put out by the ICCS [6].

Urotherapy

Urotherapy is a comprehensive term defined as a "type of training which makes use of cortical control of the bladder, teaching children to recognize and employ conscious command over their lower urinary tract". A major part of therapy for incontinence in children is non-pharmacological and nonsurgical. Its main ingredients are information about normal lower urinary tract function and the specific dysfunction in the child, instruction about what to do about it, and support and encouragement to go through with the training program [27].

Counseling

Counseling is defined as the provision of assistance and guidance in resolving personal, social or psychological difficulties. For many children, even those with psychological disorders, counseling is sufficient. Sometimes, it can be helpful to enhance the verbal counseling by other techniques. One simple technique is "demonstration", e.g. actively showing how an alarm works. In "coaching", parents and children take a more active role, e.g. they set and activate an alarm themselves. Their response can be observed and corrected. Other techniques might include "modeling" and "role-playing". The learning effect is much greater in these active forms of teaching than in solely verbal counseling.

Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is a subtype of psychotherapy that has been shown to be effective for many disorders. Cognitive therapy focuses on irrational, dysfunctional conditions, thoughts and beliefs. Cognitive therapy encompasses a whole variety of techniques such as "self-monitoring" (observation and registration), "activity scheduling" (organization of activities) and "labeling" (using positive suggestive statements). Behavioral therapy

concentrates on observable behavior, which it aims to modify using a variety of techniques that include "classical conditioning" and "operant conditioning". The latter translates into learning by success, which can be achieved by different strategies using positive or negative reinforcement.

Baseline and observation

Baseline and observation are effective techniques used in CBT. Children (and parents) are advised to observe a defined symptom. Different parameters such as frequency (how often it occurs), severity (how marked it is), symptomatology – in what form it occurs and in which situation (associated factors) – can be registered, e.g. on an observation chart. The mere observation and registration has a therapeutic effect; many symptoms diminish simply if they are observed.

In nocturnal enuresis, children are asked to fill out a calendar or chart depicting their wet and dry nights for two to four weeks. These nonspecific measures have been shown to be successful and are associated with fewer wet nights.

When urge incontinence is present, cognitive aspects are stressed during treatment: children are asked to register their feelings of urgency, refrain from using holding maneuvers, void and note their voiding (or any wetting) on a chart [28]. For children with voiding postponement, timed voiding 7 times a day and registration on a chart are recommended. For all children with encopresis, stool regulation is an essential part of treatment. Children are asked to sit on the toilet three times a day after mealtimes in a relaxed mode for five to 10 min. This is documented on a chart and can be reinforced positively. In one study, 15% of children were cured within six weeks by these simple methods [29].

Biofeedback

Biofeedback has been shown to be effective in some elimination disorders such as dysfunctional voiding [30]. It involves a variety of techniques in which physiological activity is registered, enhanced and presented to the child in real time by visual and acoustical signals [30]. In patients with fecal incontinence, biofeedback is no more effective than standard behavioral techniques whether or not constipation is present [31–33].

Alarm treatment

Alarm treatment for nocturnal enuresis is another type of CBT. It works in conjunction with positive reinforcement, as well as aversive, negative experiences, and has been shown to be highly effective after it was introduced by Mowrer and Mowrer in 1938.

It is the most effective form of treatment of nocturnal enuresis with the best long-term results (grade I level of evidence according to several reviews and meta-analyses). Houts et al. [34] compiled a systematic review and meta-analysis of 78 randomized studies on nocturnal enuresis; 62% were dry at the end of treatment and 47% at follow-up. The authors conclude that "urine alarm treatments should not only be considered the treatment of choice, but the evidence from this review suggests that cure rather than management is a realistic goal for the majority of children suffering from nocturnal enuresis". The reader is referred to the paper on monosymptomatic enuresis for details on the use of the alarm.

Non-desmopressin treatment of NMNE

The treatment of NMNE is a complex process that involves aggressive therapy for daytime issues prior to achieving success at nighttime. In this section we will discuss non-cognitive modalities to treat associated bladder problems in conjunction with enuresis. In some cases medications have been used for primary nocturnal enuresis as the initial treatment modality. In other cases some medications have never been used for nocturnal enuresis on a regular basis but are used commonly for the treatment of daytime incontinence. It is clear that the child who has a small bladder capacity has a greater risk for having problems with nocturnal enuresis. The compound risk of underlying issues that lead to nocturnal enuresis is a set-up for a perfect storm of continued nighttime incontinence. Successful management of detrusor overactivity is inversely correlated to the functional bladder capacity at night. Improper bladder emptying can also lead to elevated post void residual volumes, which in essence reduces the functional bladder capacity and leads to increased risk for nocturnal enuresis. Correction of these conditions is the primary treatment in patients with NMNE.

Bowel management

If constipation is present and a large fecal mass has accumulated, disimpaction is performed with PEG (orally), enemas (rectally) or, in extreme cases, by an extensive medical bowel cleanout at the initiation of treatment. To avoid reaccumulation of fecal matter, maintenance therapy with oral laxatives (such as polyethyleneglycol) is recommended for at least six and up to twenty-four months [35].

Elimination of elevated post void residual

Elevated post void residual is an indicator of external urethral sphincter dyssynergia, internal sphincter dyssynergia, combined internal and external sphincter dyssynergia, and/or detrusor underactivity. Identification of these conditions is critical to the proper treatment of the underlying problem. Treatment of external sphincter dyssynergia is accomplished by utilizing biofeedback therapy. Numerous studies have shown that biofeedback is efficacious in improving voiding dynamics and getting the child to void correctly and to empty. Correcting stool retention or constipation is critical. Patients with large amounts of stool have readily been identified as having increased pelvic floor activity. Lastly it is essential that a proper bowel program be initiated prior to instituting any type of biofeedback regimen. Botulinum toxin A has been utilized to treat external sphincter dyssynergia with reasonable success in

the nonneurogenic children. Internal sphincter dyssynergia is a problem that is identified primarily on uroflow/EMG, voiding cystourethrography or video urodynamics. On VCUG improper opening or funneling of the bladder neck or inability to void at the time of the study are usually surrogate markers of bladder neck dysfunction. Video urodynamics is the best means of confirming bladder neck dysfunction but this is an invasive test, which has been supplanted by the uroflow/EMG measuring lag time latencies. Prolongation of the lag time on an uroflow/EMG will help identify internal sphincter dyssynergia without the use of video urodynamics [36].

Alpha-blocking agents have been quite successful in the treatment of internal sphincter dyssynergia. The introduction of prazosin opened up a new avenue for the treatment of internal sphincter dyssynergia. Subsequently, more selective alpha-blockers have been promulgated. These more selective alpha-blockers have a greater affinity for the bladder neck [37] and they seem to be most useful when patients have primary bladder neck dysfunction with no associated bladder overactivity. When patients have associated detrusor overactivity the less selective alpha-blockers such as terazosin and doxazosin are the preferred agents to treat the overactivity and bladder neck dysfunction. Histologic studies indicate that α 1-A receptors are located primarily in the bladder neck, which are the main target of alpha-blockers, but α 1-D receptors are found in the detrusor and these are critical in modulating bladder overactivity. By choosing a non-selective alpha-blocker, albeit is possible to ameliorate overactivity without the need for an anticholinergic agent.

Internal sphincter and external sphincter overactivity does occur; in some cases this will require concomitant use of an alpha-blocker and biofeedback. In other cases if biofeedback is ineffective, the use of botulinum toxin A [38—41] injections in combination with alpha-blockers have been very useful.

Detrusor underactivity is a vexing problem. It is difficult to diagnose unless urodynamics is performed, and is almost as impossible to treat since there are no medications presently available to manage detrusor underactivity [42]. The standard treatment is the use of intermittent catheterization. A recent publication by Franco et al. [43] indicates that detrusor underactivity may be amenable to treatment with 5HT4 agonist agents. Currently no selective 5HT4 agonist is available in the United States.

Decreasing bladder overactivity

Anticholinergics

Anticholinergics have been used commonly to treat bladder overactivity. These drugs are the mainstay of treatment for this condition. In placebo-controlled studies, as identified by Cochrane Reviews, anticholinergics did not seem to have any efficacy in MNE [44]; the sole success was in children who had daytime issues. Anticholinergics are best used when overactivity has not been responsive to bowel management. It is imperative that the patient remain on some bowel management protocol to avoid constipation issues associated with the medication. Anticholinergics should be dosed based on the prescribed dose by the manufacturer. The timing of the medication is critical especially if the medication is a long acting or time released agent. An effort should be made to identify the time at which wetting is most severe (day or night), and the drug given in such a way as to match peak levels when there is maximal need for the medication.

Botulinum toxin A

In patients with detrusor overactivity refractory to all anticholinergics, botulinum toxin A injections into the detrusor have been found to be useful in clinical trials involving both adults [45—47] and children [48—51]. The primary peripheral effect of botulinum toxin A appears to be inhibition of release of acetylcholine, ATP, and substance P, and reduction in axonal expression of capsaicin and purinergic receptors. This may be accomplished by central desensitization through a decrease in central uptake of substance P and neurotrophic factors. The summation of these effects is a profound and long lasting inhibition of those afferent and efferent mechanisms that are thought to be responsible for a reduction in overactive bladder symptoms [52]. This in effect increases bladder capacity, thereby allowing for a greater bladder volume, which is essential in nocturnal enuresis management.

Centrally active medications

Centrally active agents such as imipramine were the first agents used for nocturnal enuresis. Imipramine has been found to have a direct cocaine-like effect on smooth muscle [53] aside from its peripheral anticholinergic properties [54]. For many years this was felt to be its primary mechanism of action. The active metabolite, desimipramine, is bound more to the locus coeruleus than to any other part of the central nervous system [55]. It has been postulated that the drug may have an effect on vasopressin release [56,57] and sleep modification [58]. It does not make sense that a strong anticholinergic such as oxybutynin fails when at other times imipramine, a weak anticholinergic, has a profound beneficial effect in the treatment of daytime incontinence. This dichotomy points to a different site for the action of imipramine. Most likely, imipramine is functioning in the frontal lobes at the inhibitory centers of the brain or on the default mode network [59] in children suffering from nocturnal enuresis. We have seen some beneficial effect as well with other norepinephrine reuptake inhibitors (NRI). In particular, reboxetine, which was used in refractory enuretics, had a 59% success rate in these patients [60]. There have been studies using atomoxetine, another NRI, which appear encouraging, but no other studies have been forthcoming [61,62].

Prostaglandin synthesis inhibitors (PSI) and prostaglandin receptor antagonists (PRA)

Over the years, several different PSI have been used in an attempt to reduce urine output at night so as to prevent nocturnal enuresis [63—67]. More recent research indicates there are prostaglandin receptors in the bladder [68]. Araki et al. [69] treated adults with Ioxoprofen, a non-steroidal,

and saw a reduction in nocturnal urine production and an increase in bladder capacity. This makes sense when taking into account our experience in pediatrics with ketorolac. Ketorolac has revolutionized the treatment of post-operative reimplant surgery with a remarkable improvement in bladder spasms and the overall pain experience. The concept of using prostaglandin receptor blockers and NSAIDs may be another potential avenue to increase bladder volume in patients with low daytime bladder volumes. At the present time, studies involving the use of two drugs have indicated this is not very useful in reducing urine output throughout the night, but these studies do not target patients who had NMNE. It is possible that some of these patients may have benefited had they been targeted with these PSI or PRA agents.

Advanced urotherapy

Standard noninterventional urotherapy was discussed above, describing behavioral modification and cognitive therapy as 'first-line' or 'basic' urotherapy. Treatments other than pharmacological and behavioral ones, for lower urinary tract symptoms associated or not with nocturnal enuresis, are generally adopted when the former fails to provide a satisfactory result. Despite an adequate work-up a core of 20—40% of the children with LUTD (with or without NE) at long-term follow-up are resistant to conservative treatment, including drug therapy [30,70]. Specific initial intervention used in an urotherapeutic setting for children should be non-invasive or at least as minimally invasive as possible. This includes a variety of pelvic floor re-training exercises, biofeedback and various techniques of electrical nerve stimulation that are considered a form of 'advanced urotherapy'. Traditional Chinese acupuncture or electro-acupuncture may be considered, but there is a lack of evidence for its efficacy [71,72]. The above methods of advanced urotherapy should be attempted only after exclusion of an anatomic abnormality and a neurogenic cause as a source of the LUT symptoms.

Biofeedback

Biofeedback therapy involves measuring and recording physiological processes with real-time data conversion to visible and audible stimuli that are perceptible to the patient. No strict criteria have been developed for standardized protocols of biofeedback re-training.

Factors affecting efficacy

Age doesn't seem to be a limitation. Most urotherapists agree that children as young as 5 years are capable of completing biofeedback therapy [73—75]; when comparing age against outcome, age was not a statistically significant predictor of outcome ($p = 0.5$) in the groups based on age: less than 7, 7 to 10, and greater than 10 years [76]. On the contrary, patient non-compliance due to poor motivation or managed care barriers was a statistically significant impediment to success [75]. Newer computer programs with animated pictures have achieved results in less time compared to older instruments, as they more intimately engage children in therapy [76,77].

Pelvic floor biofeedback

Biofeedback as an adjuvant method for pelvic floor re-training of dysfunctional voiding has been extensively discussed in the ICCS standardization document 'Management of Dysfunctional Voiding in Children [24]. There isn't one standard method, but the number and modality of biofeedback sessions are dependent on patient and parent(s) compliance and on local experience.

Bladder biofeedback

During bladder biofeedback children learn to sustain concentration against detrusor contraction (in overactive bladders) and to maintain a relaxed pelvic floor and voluntary external sphincter during voiding (in dysfunctional voiders). Bladder biofeedback was described 30 years ago to treat urge incontinence, frequent voiding and nocturia in women. It was successfully used to treat sensory urgency in adults [78]. The technique requires invasive intravesical filling, instructing the patient to inhibit involuntary bladder contractions by contracting the pelvic floor and external urethral sphincter, the above maneuver activating the perineal bulbar detrusor-inhibiting reflex. Due to the invasiveness of this technique (need for catheterization), it has been gradually abandoned, even though a success rate of up to 80—85% has been reported by a Spanish group with a combination of intravesical biofeedback and electrostimulation, followed by tibial nerve stimulation when the former treatment failed [79].

Electrical nerve stimulation

Electrical stimulation has been extensively investigated for over a century, as an alternative treatment for managing refractory LUT symptoms. In neuromodulation an electrical stimulus is applied to specific nerves in order to alter the presence of symptoms; the exact mechanisms are not known but the evidence indicates the site of action of this stimulation appears to involve the brain more than the peripheral organ [80—83].

In children, electrical stimulation for LUTD should be performed in a non-invasive manner. This can be done by means of transcutaneous electrodes in the region associated with the pudendal nerve, i.e. vaginal, anal [84], clitoral/penile (functional electrostimulation, FES); directly over the S2-S3 dermatomes (transcutaneous electrical nerve stimulation, TENS); or suprapubically, with the assumption that the current is applied over the affected organ [85]. While percutaneous retrograde stimulation with a 34-gauge needle is well tolerated by children, even as young as 4 years of age [86], it is feasible to use a transcutaneous electrode positioned at the same posterior tibial nerve. There are no published reports utilizing this technique. Functional extracorporeal pelvic floor magnetic stimulation has been successful in children with daytime wetting alone and with NMNE with a significant ($p < 0.05$) decrease in voiding frequency and incontinence episodes [87]. The technique is not invasive but it is very costly.

Invasive intravesical stimulation was used in a selected series of incontinent children with idiopathic detrusor

underactivity, showing long-term normalization of voiding in 83% of the cases [88]. Implantation of sacral electrodes (neuromodulation) was attempted in children with idiopathic LUTD, using a less invasive innovative technique, with limited fluoroscopy and surgery. This resulted in a low complication rate with results being presented as a response to single symptoms, and at 1—2 year follow-up a resolution/improvement rate ranging from 40 to 50% for constipation and nocturnal enuresis to 80—90% for frequency, urinary incontinence [89,90]. In spite of reports during the last two decades of clinical trials on electrical nerve stimulation to treat LUTD, the field still remains controversial due to the lack of randomized controlled studies.

The evaluation of efficacy is complicated by several factors: first, various parameters and techniques of electrical stimulation for LUTD are used; second, results cannot readily be discriminated from the contribution of concomitant interventions; third, the correct use of the devices during a home treatment is hardly measured; lastly, compliance of patients and parent(s) is variable, and the tolerable intensity is different from one child to the next. Despite these difficulties, treatment has the following advantages: it is independent of cognitive and pharmacological therapy; it is minimally invasive and free of side effects; and it is readily adapted to the home, especially using transcutaneous electrodes. The first double-blind randomized, placebo-controlled clinical trial of transcutaneous sacral (S2-S3) electrical neuromodulation in children with a refractory overactive bladder was published by the group from Aarhus [91]. They studied 27 children, aged 5—14 years, with severe urge incontinence (7 wet days per week, 1.5 incontinence episodes per day, small bladder capacity), after a minimum of 12 months of unsuccessful urotherapy and at least 3 months of anticholinergic medication. The treatment included a 2-h daily treatment for 4 weeks, using active and sham stimulation at 10 Hz frequency with a 200 μs pulse duration and biphasic waveform, with the highest tolerable current intensity of up to 40 mA. In conclusion, in children the primary goals are not only efficacy but also minimal invasiveness and practical feasibility of neuromodulation treatment in regular everyday life.

For the refractory overactive bladder, there is evidence that TENS is a reasonable alternative, when side effects of drugs become intolerable or when conventional primary urotherapy does not achieve satisfactory results. PTNS (percutaneous tibial nerve stimulation) seems promising as well, but it requires several in-hospital sessions, and no controlled studies in children are yet available. Should parents opt for non-pharmacological therapy, electrical stimulation can be proposed as a primary treatment for overactive bladder. In refractory cases, with persistent detrusor overactivity, PTNS produced good results even at long-term follow-up [92]. It can be considered as an alternative advanced urotherapy treatment.

Nonobstructive urinary retention with an underactive detrusor may be very difficult to treat, especially when psychological problems exist. As an alternative to intermittent catheterization, in selected cases, intravesical electrical stimulation may help re-establish sensation as well as improve bladder emptying by enhancing the voluntary voiding contraction. Implantation of a permanent device should be considered as a last resort in severe cases of dysfunctional voiding and dysfunctional elimination, but it should be implanted at centers that have experience with this approach.

Conclusions

The management of the child with NMNE involves a two-pronged approach, which calls for the management and identification of the underlying daytime functional bladder problem and the subsequent treatment of the nocturnal enuresis. It is critical to treat the daytime issues first and in many cases it should not even be attempted to treat the nocturnal problems, since the failure rate is high and there is a likelihood that the patient and parents will become frustrated. It is imperative for the treating practitioner to identify neuropsychiatric problems. If these are not treated at the initiation of therapy it is likely that any maneuvers to manage the daytime problems will fail and invariably the nighttime problems will persist as well.

Conflict of interest

Israel Franco is a paid consultant to Allergan, producer of botulinum toxin A. He is also a consultant to Astellas Pharmaceuticals, maker of solifenacin.

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MCQ questions

1. A 10-year-old male presents with nocturnal enuresis (NE) of new onset and a negative family history of NE. The first step in evaluating this child is to:
   a. obtain a thorough voiding history, physical examination, and treat with desmopressin.
   b. obtain a thorough bowel and voiding history, physical examination, and treat with desmopressin.
   c. obtain a thorough bowel and voiding history, physical examination, renal and bladder ultrasound, and treat with desmopressin.
   d. obtain a thorough bowel and voiding history, physical examination, and initiate a timed voiding regimen and bowel program along with maneuvers to decrease fluid intake before bedtime.
2. A 7-year-old female who has recurrent urinary tract infections and nocturnal enuresis is seen in your office for the first time. She has had a renal and bladder ultrasound and VCUG that were negative for reflux within the last 6 months, but the films are not available for your review. Physical evaluation is normal but an elevated post void residual is noted. Before embarking on managing the nocturnal enuresis the best test to do is:
   a. repeat the VCUG.
   b. renal and bladder ultrasound.
   c. uroflowmetry.
   d. uroflowmetry with a perineal EMG.

3. The previous patient was found to have external sphincter dyssynergia on the uroflow/EMG study and the VCUG revealed a spinning top urethra with a thickened and trabeculated bladder. The patient undergoes urotherapy, which includes biofeedback for 8 sessions with little to no response to elimination of the external sphincter dyssynergia. The next best treatment would be:
   a. botulinum toxin A injection to the detrusor.
   b. botulinum toxin A injection to the external sphincter.
   c. botulinum toxin A injection to the external sphincter and follow up with a new course of biofeedback therapy.
   d. alpha adrenergic blockers.
4. An 18-year-old male comes to you for a second opinion regarding his nocturnal enuresis. He also has some frequency and urgency but no daytime incontinence. He was treated in the past with desmopressin and imipramine separately with no response. He had video urodynamics, which revealed bladder neck dysfunction and a 50 cc residual.
   The next best treatment for this young man is to:

A: combine desmopressin and imipramine therapy.
B: redo the urodynamics and start the patient on oxybutynin for his urgency frequency and desmopressin for enuresis.
C: review the urodynamics and, if bladder neck dysfunction is present, start alpha-blocker therapy and reevaluate the enuresis problem after 1—2 months.
D: tell the patient that he is in the 1% that will have nocturnal enuresis the rest of his life.

5. A 10-year-old female presents for evaluation of nocturnal enuresis. She had been seen by another urologist who has treated her with an alarm, desmopressin and urotherapy, but to no avail. During your history you find out that she hates going to school and is a C-student even though her parents are on top of her to do her work all the time. She is able to sit calmly during the visit and does not exhibit any strange behavior. Both of her parents are highly successful intelligent professionals. The approach you should take is to:

A: recommend that the mother stay home with the child, since it appears that she lacks nurturing and this is the cause of the problem.
B: add oxybutynin to the desmopressin and see if this will help.
C: recommend that the child be evaluated for attention deficit disorder and if she has it, wait to see the outcome after pharmacotherapy.
D: recommend that the child be evaluated for attention deficit disorder and if she has it wait for talk therapy to be completed before attempting any further treatment.

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