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REVIEW ARTICLE

Nocturnal enuresis: A topic review and institution experience

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ABSTRACT

The objective is to provide a review of nocturnal enuresis (NE), including its epidemiology, etiology, pathophysiology, evaluation, and current management. We also set to provide further insight on the treatment of this condition from the experience derived from patients cared for at our tertiary-care institution. NE affects approximately 15% of all children at 5-year-old, affecting boys more frequently than girls. At our large university tertiary pediatric urology center, NE and incontinence, in general, is one the most common chief complaints prompting urologic care. In this review, we examine the condition in detail, highlighting specific goals of the initial evaluation and treatment. We contrast the commonly implemented treatment recommendations, available from the literature with strategies we have found valuable from our extensive experience in treating patients with this disorder. Using current urologic reference textbooks, book chapters, Medline, journal articles and reviews describing the many aspects of NE were reviewed in order to describe NE and the current practices at our institution. Although, this is not a systematic literature review, it includes relevant available research, institutional experience and urological expert opinion and current practices at a tertiary state health facility. The treatment of NE remains a challenge for many pediatricians and pediatric urologists. This likely stems from the multiple possible etiologies of the disorder. We have established a treatment algorithm at our institution, which we have found successful in the majority of our patients. This consists of starting patients on urotherapy, then offering both the enuresis alarm device and medication therapy as first line treatments, and finally adding anticholingerics for combination therapy. Our hope is with further research the treatment of NE will continue to improve.

Key words: Bedwetting, desmopressin, dysfunctional voiding, nocturnal enuresis, nocturnal polyuria

INTRODUCTION

When faced with a distraught child and frustrated parents, the challenge of treating a child with nocturnal enuresis (NE), can be overwhelming to many physicians. At our large university tertiary-care, pediatric urology center, NE, and incontinence in general, is one of the most common chief complaints prompting urologic care. In this manuscript, we review the available information on the epidemiology, etiology, pathophysiology, evaluation and current management of NE. We contrast the commonly implemented treatment recommendations, with strategies we have found valuable from our extensive experience in treating patients with this disorder.

Defining the disease

The definition of NE, accepted by most experts today and used in this manuscript, was standardized by Nevéus *et al.*, on behalf of the International Children's Continence Society (ICCS) in 2006 and updated by Austin *et al.* in 2014, in the context of an article describing the function of the lower urinary tract (LUT) of children and adolescents [Figure 1].[1,2]

Nocturnal enuresis, commonly known as "Bed Wetting", is a disorder in which episodes of urinary incontinence (uncontrollable leakage of urine) occurs during sleep in children ≥5 years of age.[2] NE can be present with or without LUT symptoms. When only NE is present, the disorder is referred to as monosymptomatic enuresis. In

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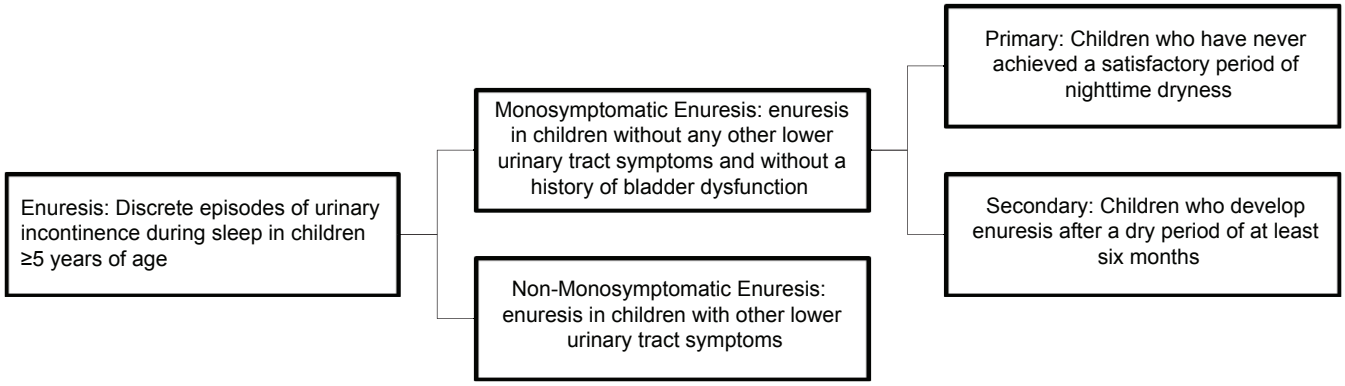

Figure 1: Defining enuresis algorithm (adapted from Austin *et al.* 2014)

the presence of other symptoms, the disorder is referred to as nonmonosymptomatic enuresis. Typically additional symptoms, in the nonmonosymptomatic enuresis patient reflect LUT dysfunction. LUT symptoms are typically: LUT pain, increased voiding frequency (≥8 times/day), decreased voiding frequency (≤3 times/day), daytime incontinence, urgency (sudden and unexpected feeling of immediate need to void), hesitancy (difficulty initiating voiding), straining (application of abdominal pressure to initiate and maintain voiding), weak or intermittent stream (weak force of urine ejection and/or micturition occurring in several discrete spurts) and spraying urinary stream.[1]

Nocturnal enuresis is subdivided into primary and secondary forms.[1] Primary enuresis is the presence of enuresis in a child ≥5 years old who has never achieved an asymptomatic period (≥6 months) of consistent nighttime dryness.[3] Secondary enuresis is the presence of enuresis in a child ≥5 years old who has achieved an asymptomatic period (≥6 months) of consistent nighttime dryness in the past.[3] Secondary enuresis is most commonly triggered by an unusually stressful life event, significant enough to cause psychosocial regression.[4]

Our discussion will elucidate ways in which a physician can delineate the type of NE a child has. We will focus our discussion on the pathophysiology and treatment strategies of children with primary NE, as secondary NE, by definition, has varying underlying mechanisms at which treatment in focused.[4]

EPIDEMIOLOGY

Nocturnal enuresis is approximately twice common in boys than girls.[5-7] It is estimated that approximately 15% of children have NE at 5 years of age, with most children, ~80%, diagnosed with primary enuresis.[3,8] NE is typically a self-limited disease, with the percentage of patients affected decreasing with age: ~15% at 5yo, 13% at 6yo, 10% at 7yo, 7% at 8yo, 5% at 10yo, 2-3% between 12-14yo and 1-2% incidence at ≥15yo.[6,9,10] It typically resolves spontaneously at a rate of 15%/year with persistence at higher ages, diminishing the likelihood that resolution will occur.[6,7,11] About 20% of these children with NE experience daytime enuresis or LUT symptoms;[12] approximately 15% of children with NE experience encopresis, the voluntary or involuntary passage of feces in inappropriate places, which shows a strong male predominance.[13]

The wide prevalence of NE speaks to the need for an improved understanding of this condition by patients, families, pediatricians, primary care doctors and urologists alike. The association of NE with many other conditions, such as: Cognitive problems, low self-esteem, attention deficit hyperactivity disorder,[14-17] and disturbed sleep,[18] enlarges the need for all clinicians to be able to recognize and evaluate patients with this disorder.

PATHOGENESIS

The necessity to identify the cause of NE is usually heightened when the clinician is faced with a new, often distressed, patient and his or her concerned parents. The potential multifactorial etiologies, encompassing psychological and physiological aspects of the disorder, frequently compromise the rapid identification of the disorder's pathogenesis.[12] The most common underlying mechanisms of NE include: Nocturnal polyuria, decreased bladder capacity (BC), detrusor overactivity, associated sleep arousal disturbances, decreased BC, global maturation delay, and genetics. NE, most likely, is a disorder caused by a combination of these etiologies in a multifactor manner.

Nocturnal polyuria

Nocturnal polyuria refers to increased urine production while asleep. The mechanism for nocturnal polyuria can

include increased fluid intake prior to sleep and/or reduced production or response to antidiuretic hormone (ADH, vasopressin).[19-24] ADH not only decreases urine production, it has also been shown to aid in the increase of bladder distention.[25] Normally, urine output is decreased during sleep, secondary to circadian changes in ADH secretion, as seen in children without NE.[26-28] There are two proposed mechanisms regarding ADH, either resistance to ADH, or a reduction in its secretion resulting in an increased urine output. Current studies of resistance to ADH have not been proven, however, nocturnal ADH secretion in children with NE has been found to be less in several studies in comparison to age-matched children without NE.[20-24] Thus, according to this theory, children with NE may not only produce more urine at night (secondary to reduced ADH), they may also have a smaller capacity for urine storage (secondary to reduced ADH effect on bladder distensibility).

Decreased bladder capacity

A normal bladder at 1 year of age has a capacity of approximately 60 mL of fluid and increases approximately 30 mL/year.[29] No anatomical differences in bladder size have been observed in children with or without NE.[25,29] However, some studies have demonstrated a reduction in nocturnal bladder function, as opposed to daytime function. Comparing the BC of children with NE, while awake, and under general anesthesia to healthy, age-matched controls they observed that patients with NE, had significantly decreased voided urine volumes in the absence of any anatomic differences.[30] Other studies have also confirmed that in children with NE, nighttime voided volumes are significantly decreased compared to daytime voided volumes.[26,31] This observation of a reduced functional BC, similar to NE itself, may have a multifactorial cause.[12]

Detrusor overactivity

The detrusor muscle plays an important role in normal voiding patterns; therefore, it has been postulated to play an important role in urinary disorders such as NE. It is theorized, that detrusor overactivity may cause bladder dysfunction in NE due to the finding that children with NE have been shown to have significantly decreased functional bladder capacities compared to healthy age-matched controls, indicating a possible lower pressure threshold for detrusor activity.[12,26,32] Children with NE, unlike patients with obstructive bladder dysfunction disorders, when studied urodynamically, do not show dysfunctional voiding patterns or high voiding pressures, indicating possibly isolated detrusor overactivity.[12] Some investigators have postulated that children with primary monosymptomatic NE may have a defect in detrusor inhibition as studies have failed to find evidence for increased uninhibited detrusor hyperactivity.[33]

Associated sleep arousal disturbances

In patients with NE, there is a basic discordance in the ability to arouse from sleep from voiding urge sensation. It is unclear whether this is caused by sleep disturbances or problems with the bladder-brain communication. There are studies that have demonstrated that children with NE have detrusor instability while asleep, but not while awake,[12,32] studies demonstrating that children with NE tend to be "deeper sleepers" than other children,[12,34-37] and other studies finding children with NE to be "light sleepers"[38] or no different than controls.[34,39]

Bladder brain connection dysfunction

One study found patients with NE to have frequent cortical arousals, but an inability to awaken completely. The cortical arousals were associated with unstable bladder contractions, suggesting to the authors that the arousal center may be paradoxically, suppressed by signals from the bladder, leading to bladder brain dysfunction. Several studies demonstrate that during sleep, children with NE have significantly less inhibition of their blink response than healthy controls.[40,41] This inhibition response is controlled by an area of the brain known as the pedunculopontine tegmental nucleus, which is located near the pontine micturition center in the brainstem; when properly treated, sleep arousals and inhibitory responses improved in children with NE. The authors concluded that a reduced ability to inhibit micturition during sleep may originate from a dysfunctional pontine tegmentum.[40,41]

Global maturation delay

Further possible central nervous system (CNS) roles in the etiology of NE have been suggested, hypothesizing neurophysiologic data support differences in the maturation of the CNS of children with NE compared to healthy controls.[32,42,43] These studies have shown that episodes of enuresis are associated with specific findings on electroencephalography (EEG) and in longitudinal studies, as children with NE age, progressive maturation of bladder stability occurs in conjunction with EEG findings that suggest increased CNS recognition of bladder fullness and the ability to suppress the onset of bladder contraction.[32] Thus, it is possible that global CNS maturation delay may be a contributor to NE.

GENETICS

It has been reported that children of parents who have experienced NE have a higher likelihood of experiencing NE.[44] Supporting a genetic contribution to the etiology of NE, Bakwin *et al.*, reported that monozygotic twins exhibit twice the risk of NE as dizygotic twins in concordance

studies.[45] These investigators also found a 75% incidence of NE in children when both parents had a history of NE, compared to 50% when only one parent had history of NE and 15% when neither parent had a history of NE.[44] An unexplained, 25-33% increased co-incidence of NE in children with sickle cell anemia has been reported compared to age-matched controls.[46] Although no genetic explanation is yet apparent, these studies and findings suggest a genetic contribution to the recognized complex etiology of NE.[46]

EVALUATION

History

The most important diagnostic step in the evaluation of a patient with urinary complaints is a thorough medical history, involving the elucidation of key information.[47] Table 1 illustrates some of the most important aspects of the history, according to Tu *et al.*, when evaluating a child with NE and correlates positive aspects of the history with their clinical significance.[48] In our experience, it is valuable to especially focus on the timing and duration of symptoms. To differentiate primary versus secondary NE, we inquire whether the child has ever had extended periods of dryness. To differentiate monosymptomatic versus nonmonosymptomatic NE, we recommend asking whether the child experiences symptoms during the day, at night, or both. To discriminate between functional versus anatomical NE, it is valuable to determine if the child has continuous leakage.[12] Along with this line of questioning, we investigate for the presence of associated symptoms (pain, urgency, frequency, holding maneuvers or situational incontinence).[49] We make it a priority to investigate the behavioral aspect of the child's urinary function, including voiding pattern, voiding hygiene, such as incomplete voiding, as well as the child's eating and drinking habits (amount and timing, content), utilizing fluid and voiding diary, in order to differentiate and assess if NE is representative of or exacerbated by excessive fluid loading. It is important to assess the child's cognitive ability; since, in our experience, functional incontinence may be confused with NE if a child has a cognitive disability. We concur with the experience of others that enuresis and stooling dysfunction are related.[50] To enhance the assessment of stooling habits we recommend the use of an objective tool, like the Bristol stool chart, for added accuracy.[50] It is also crucial to inquire whether the child is motivated to treat their condition which will help in determining first line treatment option (alarm device vs. medication). As we review the wide variety of treatment strategies for NE, it has become clear that whether or not the child is motivated to change, dramatically alters the effectiveness of these strategies.[12]

Use of a "bladder diary," the patient's (family's) own record of both voiding events and associated bladder symptoms has been recommended by the ICCS [Table 2].[1] The diary is designed to include: The timing, frequency and volumes of all voiding events (minimum 48 h), number of nocturnal episodes (7 nights), episodes of daytime incontinence (7 days), LUT symptoms (7 days), fluid intake volume/timing/content (minimum 48 h), bedtime and sleep interruptions (7 days). The use of a "bowel diary" has also been recommended by the ICCS due to the intimate relationship between bowel and bladder dysfunction and the rate of comorbidity. Like the bladder diary, the child and family are advised to record the number of bowel movements (7 days) and any episodes of encopresis, (7 days).[1] In our experience, we find these tools most valuable, as a supplement, when the history gathered is deemed either

Table 1: Important aspects of the history for a child with nocturnal enuresis

Historical feature	Possible significance
Daytime symptoms	Dysfunctional voiding
Lower urinary tract symptoms (voiding ≥8 or ≤3 times per day, hesitancy, straining, weak stream, intermittent stream, incomplete emptying, postmicturation dribble, genital or lower urinary tract pain)	Dysfunctional voiding or anatomic abnormality (e.g., posterior urethral valves)
Prolonged period of dryness (>6 months)	Secondary enuresis more often associated with psychologic comorbidities
Frequency of episodes	Nightly enuresis is associated with poor prognosis
Change in frequency of episodes over time	The natural history is of spontaneous resolution
Approximate volume of enuretic void	Estimate of bladder capacity
Fluid intake diary	May suggest etiology of nocturnal polyuria (increased afternoon/evening fluid intake; diabetes mellitus; diabetes insipidus; psychogenic polydipsia)
Stooling history	Constipation may contribute to decreased bladder capacity
Review of systems	May identify previously undiagnosed medical condition that contributes to enuresis
Snoring	Obstructive sleep apnea
Weight loss, fatigue	Diabetes, kidney disease
Gait abnormalities	Spinal dysraphism
Staring spells	Seizure disorder
Perianal itching, vulvovaginitis	Pinworms
Excessive thirst, nighttime drinking	Diabetes, kidney disease, psychogenic polydipsia
Family history of enuresis	Genetic factors may be contributing

insufficient or unreliable. We have also experienced difficulty with adherence by both the child as well as their families.

In addition to the previously described history, the ICCS recommends the use of questionnaires in order to quantify the symptomatology of both the LUT symptoms and emotional impact on the patient.[1] In patients where intellectual or behavioral disorders are suspected, the use psychological screening may be beneficial.[1]

Physical exam

The diagnosis of primary monosymptomatic NE will most likely be made from the history alone, however, the physical exam always proves helpful particularly when the etiology of the patient's symptoms is secondary to an underlying medical condition or anatomical abnormality.[19,48,51,52] Table 3 lists the most important aspects of the physical exam when evaluating a child with NE and correlates positive aspects of the history with their clinical significance.

Table 2: Neveus 2006 urodynamic instruments used for children

Urodynamic instruments in children		
Instrument	**Age**	**Data**
Bladder diary	From 5 years	Voided volumes Voiding frequency Urine output Symptom (leakage, etc) frequency Other data (Appendix 5)
Uroflow and residual	From 5 years	Voided volume Curve shape Urine flow rate Residual urine
Cystometry	All ages	Detrusor pressure and activity Cystometric bladder capacity Compliance Sphincter competence and activity Other data (see specific section)
4-Hour voiding observation	Infancy	Voided volumes Voiding frequency Residual urine Observation of symptoms

Table 3: Important aspects of the physical exam of a child with nocturnal enuresis

Examination finding	Possible significance
Poor growth	Renal disease
Hypertension	Renal disease
Wetness in the undergarments	Daytime incontinence
Palpation of stool in abdomen	Constipation
Perianal excoriation or vulvovaginitis	Pinworms
Abnormalities of lumbosacral spine (midline hair tuft, abnormal gluteal fold)	Spinal dysraphism
Incomplete bladder emptying (by percussion or palpation)	Urologic abnormality
Observation of slow urinary stream, straining, dribbling, intermittent stream	Urologic abnormality
Abnormal neurologic examination of the perineum and lower extremities	Spinal cord abnormality

Investigations

If the child's history is not clearly primary monosymptomatic NE, it is reasonable and recommended to have the child undergo further investigation [Figure 2].[53] A urine analysis (UA) can be obtained as a screening tool for possible medical conditions such as: Infection, diabetes mellitus or insipidus.[51] If the results of the UA indicate possible infection, urine culture is then indicated. If the history and physical exam have raised the suspicion of urinary obstruction, structural abnormalities, recurrent infection or significant daytime symptoms, a postvoid residual volume (PVR) and bladder/renal ultrasound should be obtained.[51] According to the ICCS guidelines, a normal PVR in a child, whom you expect to have the capability of emptying their bladder completely, is age dependent. Children 4-6 years old, with a single PVR 30 mL or >21% of estimated BC or repeated PVR > 20 mL or >10% of BC is abnormal, and children 7-12 years old with a single PVR 20 mL or >15% BC or PVR > 10 mL or >6% of BC is abnormal.[1] Initial imaging of the urinary anatomy with renal and bladder US is indicated, if there is a high suspicion of an anatomic anomaly, spina bifida occulta or neurogenic bladder.[54] Further imaging with magnetic resonance imaging and/or urodynamic studies may become indicated [Figure 2].[54] Other more invasive investigations, such as: Voiding cystourethrogram, retrograde urethrogram and urodynamic testing, while outside the scope of this review, are indicated in certain instances, like spinal cord anomalies or frequent urinary tract infections.

Almost all children seen at our institution for NE are referred to us by their primary care physician having failed initial treatment. No further investigation is usually required before we feel comfortable enough to begin both a diagnostic and therapeutic treatment trial.

TREATMENT

We will focus on the treatment strategies for primary monosymptomatic NE, as the treatment for secondary NE, involves treating the underlying stressor or medical condition causing the regression, and if no cause can be identified, these patients are treated in the same fashion as children with primary NE.[48,51]

Behavioral

In our experience, first line treatment for both our patients and their families is education. NE can be a frustrating and

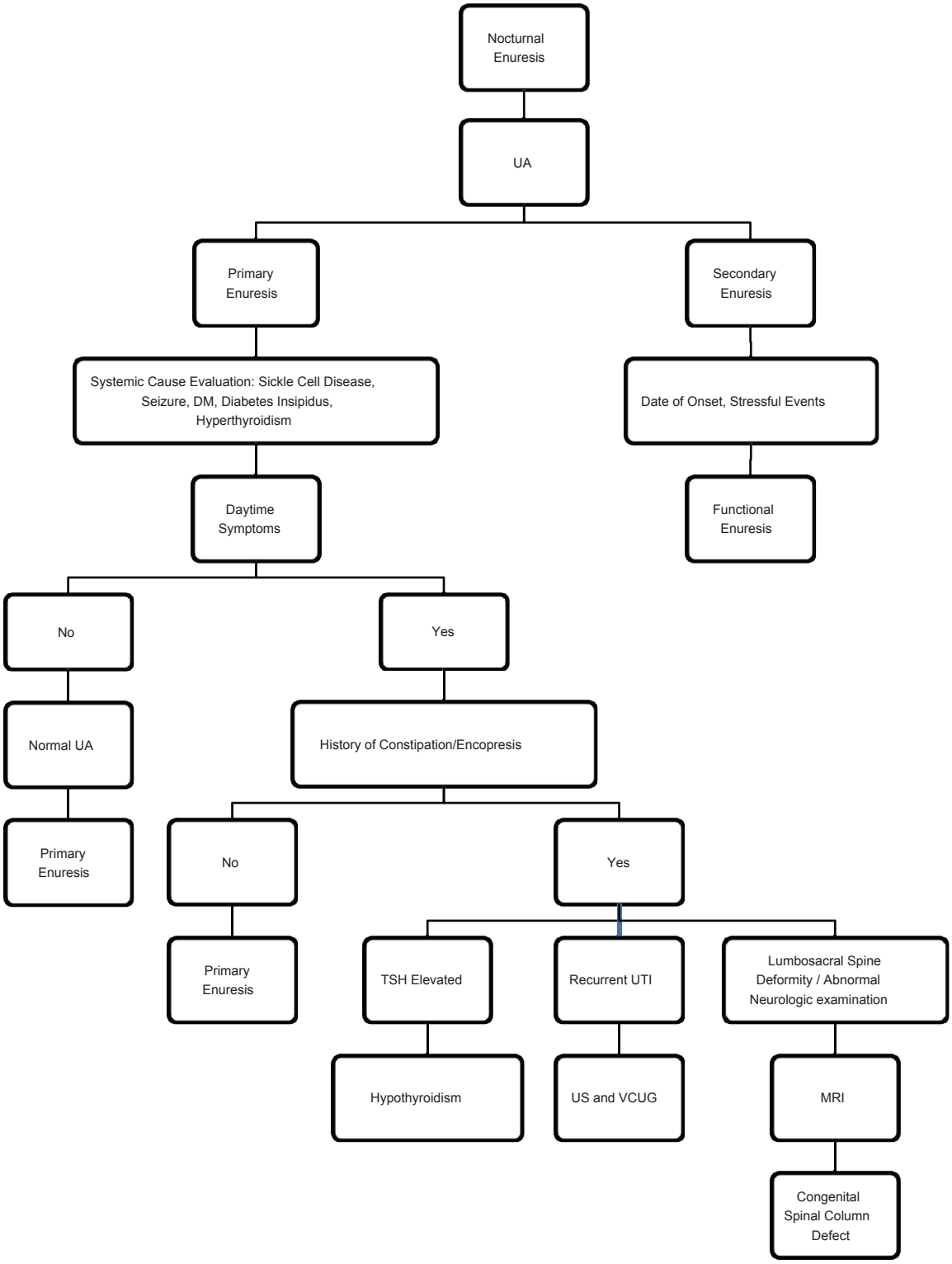

Figure 2: Nocturnal enuresis algorithm (adapted from Gomelia LG. Nocutrnal Enuresis Algorithm. The 5-Min Clinical Consult 2013. Lippincott Williams and Wilkins, May 18, 2012)

embarrassing condition for patients and their families alike.[55,56] Taking extra time to educate, reassure, and fully answer questions of the children and their caretakers about NE is of the utmost importance. As previously stated, the majority of children with NE will have spontaneous resolution, such that education and reassurance involves not only prognosis, but also the setting of goals. The ICCS guidelines define response to treatment in terms of initial success and long-term success [Table 4], which can be helpful in define treatment goals.[1] In general, the goal of NE treatment will include:

Reducing the total number of enuretic nights, avoiding enuresis on specific nights in specific locations, stress reduction for the child and family and the avoidance of NE recurrence.[48,57,58]

The next step in the treatment for NE is behavioral therapy, also known as urotherapy. Urotherapy is a nonpharmacologic and nonsurgical treatment for NE which includes education on: Normal bladder function, normal voiding habits, how the child differs from normal, and how to change voiding behavior (posture, timing, holding maneuvers). This is especially beneficial in nonmonosymptomatic NE to normalize the function of the bladder during the daytime, which will improve the function at night as well. Urotherapy involves advice regarding fluid intake and the avoidance of constipation, support for the family and caregivers when needed, and regular follow-up appointments.[1]

We instruct our patients to begin timed voiding once every 3-4 h. We also advise our patients to stay hydrated, but to shift fluid intake habits by drinking 2/3rd of their normal total daily fluids during the morning to early afternoon and then other 1/3rd the remainder of the day. We also advise a decrease in the amount of diuretic fluids the child may drink, that is, coffee, tea or soda. It is also important to us that the child stops all fluid intake 1-2 h before bedtime, and empty his or her bladder immediately before bedtime. At our institution, if the patients and their families have not already done so, they are advised to keep both a bladder and bowel diary during the time between their next visit.

Motivational therapy (positive reinforcement), prizes or stickers for following the urotherapy guidelines and for periods of extended dryness, is helpful for children who are motivated to treat their NE.[59] In children between 5yo and 7yo with mild symptoms (enuresis <7 nights/week), this type of intervention has been shown to be 25% effective with a relapse rate of approximately 5% and reported symptom improvement in 80% of patients.[48,59-65]

It should be stressed that punishment (negative reinforcement) is NOT an acceptable treatment option. Punishment is not only ineffective, it can counterproductive by enhancing stress related accidents and at its worst, abusive.[51,55,56,59,66,67]

Table 4: Defining treatment success Austin *et al.* 2014

Success type	Term	Definition
Initial	Nonresponse	0%-49% decrease in symptom frequency
	Partial response	50%-99% decrease in symptom frequency
	Full response	100% decrease in symptom frequency
Long-term	Relapse	>1 symptom recurrence in 1 month
	Continued success	≥6 months without relapse off of treatment
	Complete success	≥2 years without relapse off of treatment

Alarms

In general, clinicians allow 6 weeks to evaluate the effectiveness of behavioral and motivational therapy before implementing more invasive treatment strategies. If behavioral therapy is ineffective after 6 weeks, the addition of enuresis alarms is appropriate.[51,68,69] Enuresis alarms are electronic devices that are worn or placed in bed that will provide a signal, most commonly loud acoustic noise, when it senses an episode of incontinence.[1] Meta analyses have shown enuresis alarms up to 66% effective, noninferior to Desmopressin and more effective than tricyclic antidepressants (TCAs) in children who are motivated and have the cognitive capacity to understand the alarm system.[68,70,71] However, several studies have demonstrated compliance difficulties with these devices, for various practical reasons including cost, difficulties in set up, and discontinuing the use due to: Failure of the alarm to wake the child, false alarms, alarm failure and skin irritation.[58,72,73]

At our institution, patients are typically referred after pediatricians and primary care physicians have begun preliminary treatments. Generally, patients have already tried behavioral therapy, urotherapy therapy and in many cases either failed or declined alarm device for several reasons. We also observed a cultural bias against alarm devices in many cases. In addition to the above difficulties, we encounter concerned families regarding multiple sleep interruptions possibly being detrimental to the child. Based on those practical difficulties and possible side-effects based on our observation and experiences from families regarding discussion about alarm device treatment, we have created our own treatment algorithm to fit our population [Figure 3]. However, with the advent of and wide availability of "smart" phones, the use of applications may aid and ease the use of alarms, and may be an area of research in the future.[1]

Medications

Desmopressin (DDAVP) is a synthetic ADH, and in tablet or nasal form, is indicated for children >5 years old with NE refractory to urotherapy.[74] In addition to alarm therapy, desmopressin therapy is recommended as first line treatment for patients with primary monosymptomatic NE with an International Consultation on Incontinence (ICS) level 1 grade A recommendation.[75,76] DDAVP is generally considered to be a relatively benign medication, especially at low doses,[76] however, a base line CMP may be advised because DDAVP is contraindicated in children with a history of hyponatremia.[77] According to the literature, DDAVP monotherapy has been shown to achieve total success in as much as 30% of children, with an additional 40% experiencing significant improvement.[51,69] However, studies comparing its effectiveness to enuresis alarms have demonstrated a

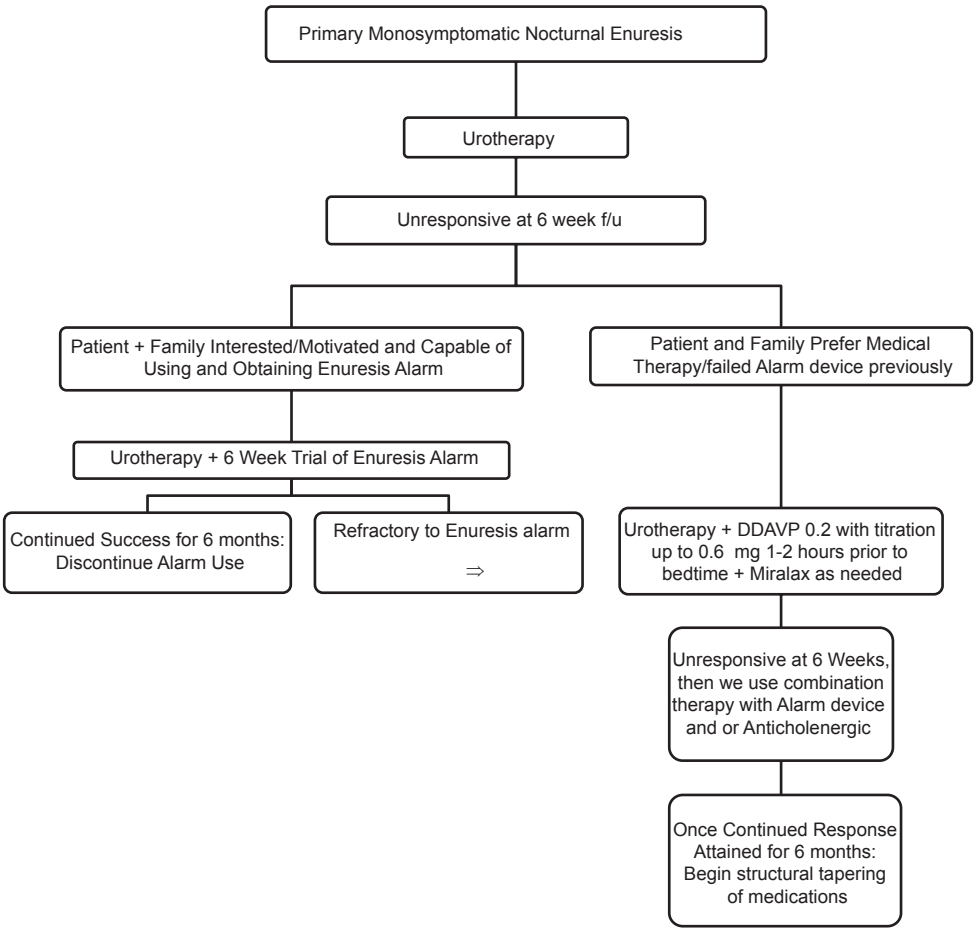

Figure 3: Primary nocturnal enuresis treatment algorithm

recurrence rate of up to 70% following discontinuation.[71] Conversely, more recent studies have shown Desmopressin treatment with a structured medication withdrawal protocol may have superior response rate than those from alarm therapy alone.[76,78] We have observed similar results, thus we recommend tapering off the dose of DDAVP, as the risk of recurrence has decreased in our experience.

After initial failure or recurrence after monotherapy with either DDAVP or alarm device, combination therapy of DDAVP and alarm device has shown to be helpful in children with severe symptoms, behavioral and familiar difficulties.[79] However, other studies have demonstrated that DDAVP does not enhance alarm response.[80] This is an area of continued discussion and hopefully the subject of future research.[51]

Anticholinergic medications, such as oxybutynin (Ditropan) have been used to treat urinary urgency, frequency and incontinence.[81] Anticholenergic medications act by relaxing the smooth muscles of bladder increasing BC.[81] Little literature exists on anticholenergic monotherapy, as it is not considered first line therapy,[82,83] however there are several studies examining combination therapy of DDAVP with anticholenergic medication.[84,85] These studies have found this combination therapy is both safe and effective (57-66%) in children refractory to initial therapies.[84,85] In our practice, we have not seen benefit from anticholinergic medications alone in treating monosymptomatic NE. We do, however, use oxybutynin in combination with DDAVP in attempts to relax the bladder to provide more bladder capacitance, especially in patients with daytime LUT symptoms. This strategy has shown benefit in our experience, consistent with the literature.[34,35,84-86] There is concern about anticholinergic side effects, specifically constipation.[81] Similar to all of our patients, these patients, especially those constipated, are started on a stool softener (Miralax).

For children with NE refractory to behavioral therapy, DDAVP and anticholinergic therapy, imipramine, a TCA is indicated.[87] It has demonstrated a 20% complete success rate in treating NE compared to the placebo response of 5% (P =0.05), however, a relapse rate of 96% when the medication was discontinued.[51,88,89] Imipramine, as well as all other TCAs, have a black box warning of increased suicidality.[77] It is for this reason, and others, such as, the risk of overdose,

concomitant constipation, cardiotoxicity and its relatively limited efficacy, that we do not recommend Imipramine therapy to our patients, unless absolutely necessary.[87]

As previously stated, both urinary and bowel dysfunction are associated.[90] Encopresis is discussed extensively in the literature, in our population we observed a large percentage of children suffering from NE to have comorbid constipation. Miralax (Polyethelyne Glycol 3350 OTC), a balanced polyethylene glycol, is a nonabsorbable osmotic laxative that has been shown not to cause significant fluid or electrolyte shifts; it is therefore safe to be used for patients in all age groups.[90,91]

CONCLUSION

The treatment of NE remains a challenge for many pediatricians and pediatric urologists. This likely stems from the multiple possible etiologies of the disorder. We have established a treatment algorithm at our institution, which we have found successful in the majority of our patients [Figure 3]. This consists of starting patients on urotherapy, decreasing diuretic fluids intake, stopping fluid intake 1-2 h before bedtime, and emptying their bladder right before bedtime. Most patients presenting to our institution have already been advised to make these changes and have either seen no response or have been unable or unmotivated to adhere to all of the recommendations. We then educate our patients and their parents about other treatment options including enuresis alarms or medication. Most of our patients and their parents opt for medication for different reasons. We advise continuing urotherapy and at the same time we start DDAVP 0.2 mg 1-2 h prior to bedtime, titrating the dose once every 1 week up to 0.6 mg based on clinical response. We start patients on a Miralax, as constipation is commonly a contributing factor. If the NE continues we discuss combination therapy with alarm device or weight based anti-cholingerics to the regimen. All medications are weaned off in the same manner they were started to help decreased the rate of recurrence. Finally, our hope is in the future with further research we will continue to improve the treatment NE.

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