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EDUCATIONAL REVIEW

Nocturnal enuresis—theoretic background and practical guidelines

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Abstract Nocturnal polyuria, nocturnal detrusor overactivity and high arousal thresholds are central in the pathogenesis of enuresis. An underlying mechanism on the brainstem level is probably common to these mechanisms. Enuretic children have an increased risk for psychosocial comorbidity. The primary evaluation of the enuretic child is usually straightforward, with no radiology or invasive procedures required, and can be carried out by any adequately educated nurse or physician. The first-line treatment, once the few cases with underlying disorders, such as diabetes, kidney disease or urogenital malformations, have been ruled out, is the enuresis alarm, which has a definite curative potential but requires much work and motivation. For families not able to comply with the alarm, desmopressin should be the treatment of choice. In therapy-resistant cases, occult constipation needs to be ruled out, and then anticholinergic treatment—often combined with desmopressin—can be tried. In situations when all other treatments have failed, imipramine treatment is warranted, provided the cardiac risks are taken into account.

Keywords Enuresis · Incontinence · Enuresis alarm · Desmopressin · Anticholinergics · Imipramine

Introduction

Even though the days are long since passed when enuresis was considered a neurotic disorder and the primary treatment was psychotherapy—or no therapy at all—there is still some controversy regarding both its pathogenesis and treatment.

The purpose of this review is first to give a theoretical background and then, based on this background, to provide practical guidance. Throughout the text the new terminology of the International Children's Continence Society (ICCS) [1] will be strictly adhered to, i.e. enuresis will be taken to denote urinary incontinence while asleep in a child aged at least 5 years.

Background: epidemiology, etiology and pathogenesis

Enuresis is a common condition. Approximately 5–10% of 7 year-olds regularly wet their beds [2], and the problem may persist into teenage and adulthood. Boys are more commonly afflicted than girls [2], and the condition tends to run in families. There are three pathogenetic mechanisms that have sufficient scientific support to be regarded as important, namely, nocturnal polyuria, nocturnal detrusor overactivity and high arousal thresholds. These may all, in turn, be explained by a common underlying disturbance at the brainstem level.

It is quite evident that there are bedwetting children who produce disproportionately large amounts of urine at night; this polyuria is often explained by a nocturnal lack of the antidiuretic pituitary hormone vasopressin [3]. It is also known that bedwetting can be provoked in some non-enuretic children just by having them drink lots of water before bedtime [4] and that the vasopressin analogue desmopressin makes many bedwetters dry—especially the ones with polyuria [5]. There are, however, some important modifications to the hypothesis. First, not all bedwetting children are polyuric [5]; second, some dry children are polyuric (and have nocturia instead of

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enuresis) [6]; third, the polyuria does not explain why the children do not wake up.

Many enuretic children wet their beds not because their bladders are full but because they suffer from nocturnal detrusor overactivity. Indirect evidence for this is the great overlap between nocturnal enuresis and urgency or urge incontinence [7] and the fact that enuretic children—especially the non-polyuric ones—void with smaller volumes than non-enuretic children [8]. Direct proof comes from ambulatory cystometries of children with therapy-resistant enuresis [9].

It is often stated that the nocturnal bladder *volume* is reduced in enuretic children. This statement is true but also quite misleading. The bladder is not *anatomically* small, but it tends to contract before it is full. Both bladder distension and detrusor contractions are strong arousal stimuli [10]. Thus, the bedwetting child can be regarded as a "deep sleeper" almost by definition, which is also supported by the quite universal parental observation that their enuretic children are difficult to wake up [11] as well as by studies on objective arousal thresholds [12]. This does, however, not mean that the sleep electroencephalogram (EEG) of enuretic children is necessarily different from that of dry children. This disorder of arousal may have underlying brainstem explanations, or it may, paradoxically, be caused by the arousal stimuli themselves. If somebody (in this case, the full or overactive bladder) is always knocking at the door, you end up by ignoring it or even installing an extra lock.

In summary, the enuretic child (or adult) wets his/her bed because either (1) bladder (over-)filling fails to wake him/her up or (2) uninhibited detrusor contractions fail to wake him/her up or (3) both.

Interestingly, there is increasing evidence that all three mechanisms can be attributed to an underlying brainstem disturbance. The locus coeruleus (LC), a noradrenergic neuron group in the upper pons, is crucial for arousal from sleep [13] and overlaps both functionally and anatomically with the pontine micturition center [14], which coordinates the micturition reflex. The LC also has axonal connections with the hypothalamic cells that produce vasopressin [15]. Evidence implicating a disturbance in this region of the brainstem in enuretic children is accumulating [16, 17].

Finally, it is important to recognise that enuresis can, in a minority of cases, be caused by other diseases. Polyuric conditions such as diabetes—mellitus or insipidus—or nonoliguric renal failure are classical examples. Most patients with these conditions do *not* become enuretic [18], but some certainly do. Urinary tract infection (UTI) can also cause enuresis or urge incontinence, but most often the latter condition. The same is even more true for constipation [19]. One reason for this association is probably the fact that the filled rectum compresses the bladder, causing detrusor overactivity. The child with neurogenic bladder may certainly wet his/her bed, but enuresis would probably not be the only symptom. Among urinary tract malformations that may cause enuresis, the urethral valves deserve special mention. Those boys with urethral valve malformation not only have a disturbed bladder function but also renal tubular damage that leads to vicious circles of polyuria, increased intravesical pressure and yet more renal damage.

Enuresis may be caused by heavy snoring or sleep apneas due to adenotonsillar hypertrophy. There are two, non-exclusive, possible explanations for this: first, the constant arousal stimuli from the obstructed airways causes paradoxically high arousal thresholds and, second, the negative intrathoracic pressure causes polyuria via increased secretion of the atrial natriuretic peptide [20].

Treatment: theoretical considerations

The available antienuretic treatment alternatives can be logically classified according to which underlying pathogenetic mechanism they address.

Desmopressin is a vasopressin analogue that retains the hormone's antidiuretic effects. It has been used for several decades and has a proven antienuretic effect [21]. As a rule of thumb, one third of unselected enuretic children are reliably dry as long as they take the drug, one third has a partial response and one third is not helped at all. It is logical to assume that the reason for desmopressin's antienuretic effect is reduced urine production, and this assumption is strongly supported by the fact that the presence of nocturnal polyuria is a positive prognostic indicator [8]. There is, however, also some evidence that central nervous system effects may be active as well [22].

Desmopressin is remarkably free of risks and adverse effects, even if used for months and years [23], but potentially dangerous hyponatremia may result if the drug is combined with excessive fluid intake [24].

The first-line treatment of daytime incontinence in childhood is basic urotherapy, i.e. advice regarding fluid intake and regular voiding habits. The same advice is routinely given to enuretic children as well [25]. This is not illogical, given the role of detrusor overactivity in enuresis, but to date evidence for the efficacy of this approach is weak [26–28]. However, urotherapy is certainly not harmful and alleviates concomitant daytime symptoms.

It is also logical that anticholinergics, the established second-line therapy against urge incontinence, have been used in enuresis. The initial results have been only modestly encouraging [29, 30], but there is now evidence

that the anticholinergic drug tolterodine is in fact useful as an add-on therapy in enuretic children who have not responded to desmopressin alone [31]. The drugs oxybutynin, tolterodine and propiverine are the most widely used alternatives; they are not toxic but do carry a real risk for constipation and for UTI due to the accumulation of residual urine. In the case of oxybutynin, psychiatric side effects are also not uncommon [32].

The inability to wake up from sleep is addressed by the enuresis alarm. The underlying concept is simple: the first drop of urine that reaches a detector in the bed or the underclothes elicits a strong (usually acoustic) arousal stimulus, thereby gradually teaching the patient to wake up instead of wetting the bed. It is, however, still unclear why the alarm works. And in fact, most of the enuretic children who are successfully treated with the alarm do *not* then start to wake up and exchange enuresis with nocturia [33]. Despite this, the efficacy of such alarm treatment is proven, the response rate varies between 50 and 80% depending on the population chosen [34], and most children successfully treated can be considered to be cured [35]. Not surprisingly, the chance for successful alarm therapy is greatest if the child and family are well motivated.

The tricyclic antidepressant imipramine has been successfully used as an antienuretic therapy. Placebo-controlled studies give a response rate of approximately 50% [36]. The reason for this effect is also far from clear, but it is most likely that the antienuretic potential is linked to brainstem noradrenergic action [37]. Imipramine is now (hopefully) only used in severely therapy-resistant enuresis, since side effects—mostly mood changes, which can be bothersome—are common, and overdosage can prove fatal [38].

Finally, alternative treatment modalities, such as acupuncture and hypnotherapy, are often advocated. Sadly, the evidence base for these therapies is, as yet, not firm enough to warrant their use as standard therapies [39–41].

Comorbidity and consequences

All enuretic children do not grow out of their condition. Prevalence figures for enuresis in adulthood vary between 0.5 and several percent [42, 43]. The risk for the enuresis persisting into adulthood is highest in children who wet their beds every night [44]. The enuretic child is also at risk of developing other bladder problems, such as urge incontinence, in adulthood [45, 46].

Furthermore, the psychosocial consequences of enuresis can be grave. The links between the bladder and the soul are problematic to disentangle due to the difficulty of knowing what is cause, what is effect and what is comorbidity without a direct causal relationship. However, this much is clear:

1) Enuretic children suffer from low self-esteem as long as they continue to wet their beds [47].
2) Enuresis—as well as daytime incontinence—is more common among children with neuropsychiatric disturbances, such as attention deficit hyperactivity disorder (ADHD) [48]. Among children with enuresis, approximately 15% have ADHD, and vice versa [49, 50].
3) Enuretic children and adults have, in general, more depressive problems and problems at school and work [43].
4) The enuretic children with highest risk for psychosocial comorbidity are those with nonmonosymptomatic, secondary or therapy-resistant enuresis [51].

Practical guidelines

The following recommendations are designed to be cost-effective and applicable even in a situation with limited healthcare resources. Extensive, time-consuming evaluations are thus limited to children with suspected underlying disorders and those who have proven to be therapy-resistant. The advice is adapted from the official ICCS guidelines for the evaluation of monosymptomatic enuresis [25].

Evaluation at the first visit

The first healthcare professional to see the enuretic child may be a paediatrician, a general practitioner or a nurse. What matters is that the person who sees the child knows which questions to ask. The purpose of the first consultation is to detect whether extra evaluation or specialist consultation is needed, to decide whether the child should be treated at all, and then, optimally, start treatment. To achieve this a basic case history and the results of a urine dipstick test are needed. The history should focus on general health, bladder and bowel habits and psychological factors. A minimum list of suggested items is provided in Table 1. The use of a proper bladder diary will substantiate history data, help in the detection of bladder dysfunction and detect families with poor compliance.

No radiology and no urodynamic investigations are compulsory at this stage. Even a physical examination is not necessary—provided the healthcare provider reacts to warning signs in the case history and/or the results of the urine test. The relevant warning signs, and the actions to be taken if present, are listed in Table 2. If none of these factors apply and the child is old enough to be bothered by his/her problems, then active treatment can be initiated. This approach means that most children aged 6–7 years or older, but only very few 5 year-olds, should be treated actively.

Table 1 Relevant patient history at the first consultation

Areas of interest	Relevance
General health and development	
Growth, weight loss	Poor growth in renal failure. Malaise, nausea, weight loss etc in diabetes or kidney disease
Micturition and drinking habits	
Bedwetting frequency	Poor prognosis in very frequent enuresis
Previous dryness	Comorbidity (somatic or psychiatric) more common in secondary enuresis
Daytime incontinence: When? How often?	Urge incontinence should be treated before enuresis. Neurogenic or anatomic causes gives daytime incontinence more often than isolated enuresis.
Urgency	Indicates detrusor overactivity
Weak stream, hesitancy, straining	These symptoms may indicate neurogenic bladder or malformation
Urinary tract infections	Indicates lower urinary tract dysfunction, neurogenic bladder or malformations, most commonly the former
Excessive thirst. Need to drink at night	Kidney disease, diabetes or habitual polydipsia. Desmopressin contraindicated.
Bowel habits	
Bowel movement frequency, stool consistency.	Low stool frequency and/or hard stools indicate constipation, which should be addressed before enuresis treatment can start
Faecal incontinence	This is most commonly caused by constipation.
Psychology	
Behavioral problems	If behavioural problems are severe they may need to be addressed concomitantly with enuresis therapy
How does the child view his/her enuresis?	The child who is not bothered by the enuresis may not be motivated for labour-intensive therapy

First-line treatment

If the child also suffers from bothersome daytime incontinence this should be treated first. Otherwise, the first treatment, for the family who is well-motivated and well-informed, is the enuresis alarm. Desmopressin is the first-line treatment for families who are not sufficiently motivated to use the alarm, who have recently used the alarm (correctly) without success or who are considered unlikely to comply fully with alarm treatment. If measurements of daytime voided volumes and nocturnal urine production during "wet" nights (with weighing of diapers or sheet covers) have been performed and the child is found to have low voided volumes [maximum voided volume <70% of the expected bladder capacity (30+30 × age mL)] and no nocturnal polyuria (nocturnal urine production less than 130% of the expected bladder capacity), then desmopressin will probably not be useful.

Table 2 Factors indicating that further evaluation is needed before the enuresis can be addressed

Warning signs	Actions to be taken
Daytime incontinence or urinary tract infections.	Make the family complete a frequency-volume chart before proceeding. Treat daytime incontinence before enuresis.
Faecal incontinence, hard stools, unfrequent bowel movements	Suspect, and treat for, constipation
Significant problems with peer relations and behavior	Risk for therapy-resistance and/or psychiatric comorbidity. Consider parallel psychological evaluation.
Straining, weak stream, continuous incontinence	Suspect neurogenic bladder or anatomic abnormalities. Send to secondary center.
Glucosuria	Consider diabetes mellitus. Check blood glucose immediately
Proteinuria (++ or more on urine test)	Consider kidney disease. Consult paediatrician
Leukocyturia or nitrite test positive	Take urine culture. Consider antibiotic treatment if culture is positive
Excessive thirst, need for night-time drinking	Consider polydipsia or kidney disease. Measure fluid intake
Nausea, weight loss, fatigue	Consider kidney disease. Check creatinine, hemoglobin and electrolytes and consult paediatrician.

There are a few important rules for successful enuresis alarm treatment:

1) A parent should sleep in the child's room and help him/her get up immediately when the alarm goes off. Very often, the child will not be able to wake up by him/herself during the first weeks of treatment.
2) Treatment needs to be continuous; no weekend alarm holidays!
3) The instructor should provide frequent follow-up, with a first phone call after 2 weeks, with the aim to provide encouragement and solve technical problems.
4) If there is no positive effect after 6–8 weeks, then treatment should be stopped. Otherwise, it should continue until 14 consecutive dry nights have been achieved.

If desmopressin treatment is chosen, it is recommended that the oral quick-melt formula be used. The initial dosage is 240 ug—to be taken 0.5–1 h before bedtime. A positive effect will be seen directly; the lack of a beneficial effect after 1–2 weeks of therapy means that treatment should be stopped. If, on the other hand, the response is good, then the dosage should be lowered to 120 ug to determine whether this is enough to keep the child dry. Continuing treatment—for those who respond—can be given every night or just before "important nights" at the discretion of the child and family. If continuous treatment is chosen, then regular drug-free intervals should be interspersed to check if the medication is still needed. In order to eliminate the risk for hyponatremia, the child should be instructed to limit fluid intake to a maximum of 2 dL from 1 h before medication until the next morning. The only contraindication to desmopressin therapy is habitual polydipsia.

If the first choice of therapy, either the alarm or desmopressin, did not work, then the other alternative should be tried, but then first a full bladder diary with measurements of noctunal urine production should be completed. The child who has failed desmopressin therapy and is now found to have nocturnal polyuria should combine the alarm treatment with desmopressin to improve the chance of success.

Evaluation of therapy-resistant children

If neither the alarm nor desmopressin has helped, then the child needs to se a paediatrican or paediatric urologist and undergo a general physical examination, including an examination of tendon reflexes and the lower back, in order to find signs of spinal dysraphism. If a bladder diary has not been completed before this step, it should be done now, including measurements of nocturnal urine production.

Symptoms and signs of constipation should be actively sought. A rectal examination should be performed if the anamnesis gives any suspicion of constipation (infrequent bowel movements, hard stools, faecal incontinence)—provided the child and family are reasonably comfortable with the procedure—since faeces in the *ampulla recti* is almost pathognomonic.

The family also needs to be asked about the presence of heavy snoring or excessive thirst (especially the need to drink at night). Both fluid intake and creatinine as well as urine osmolality should be measured in the child with suspected polydipsia. The perceived reason for failure with the enuresis alarm should also be asked for, since it is very common that the family has not been given correct advice (see above).

Uro-flow and residual urine measurements should be performed in order to detect signs of outflow obstruction or neuropathic bladder and to check for contraindications to anticholinergic treatment (persistent residual urine).

Evaluation of the upper urinary tracts are usually not indicated, but ultrasonographical measurement of the horizontal rectal diameter is very useful [52]. A diameter of more than 3 cm indicates constipation.

Cystometry, cystoscopy and further radiologic evaluations are still not necessary, provided the above-mentioned examinations do not reveal signs of neurological disturbance, renal damage or bladder outlet obstruction. Blood tests will also not provide much useful information.

Secondary therapy

Constipation, if suspected, should be treated first as this will either cause the enuresis to disappear or else make other antienuretic therapies more likely to succeed.

Anticholinergic treatment is then the treatment of choice. Although in many countries oxybutynin is currently the only such drug registered for label use in children, tolterodine is perhaps a better choice, since this drug has fewer central nervous side effects. When more drugs have been thoroughly tested in children, this recommendation may change. Anticholinergic therapy has the greatest chance of success in the child with signs of detrusor overactivity, i.e. low daytime voided volumes. Before anticholinergic treatment is started, constipation and residual urine need to be excluded or treated, and the family should be instructed to look out for UTI symptoms.

Tolterodine can be used at a starting dosage of 2 mg, regardless of age, given 1 h before bedtime. A positive response will be seen within 1–2 months. If the response is unsatisfactory but side effects are mild or absent, then the dosage may be increased to 4 mg and desmopressin added to the drug regimen. The successfully treated child should taper therapy at least three to four times per year until he/she stays dry without drug treatment. If treatment is initially successful but later more and more wet nights start to reappear, faecal impaction should be suspected and treated.

In a bedwetting child who is reported to snore heavily or experience nocturnal apnoeas, tonsillectomy and/or adenoidectomy should be considered as a possible treatment.

The help of a psychologist or child psychiatrist should be sought when it is suspected that there are behavioural issues (ADHD, for instance) that make successful antienuretic therapy difficult or when the psychological problems are grave enough to merit treatment regardless of the enuresis. The child who is anxious or has a low self-esteem because of the wetting is best treated by making him/her dry!

If desmopressin, the alarm and the anticholinergic treatment have all been tried without success, or have been judged unsuitable, the cautious use of imipramine is warranted. This is, however, a matter for specialist clinics and not for the general paediatrician. Imipramine should never be prescribed to a child with a history of unexplained syncope/palpitations or with unstable arrhythmias or sudden cardiac death in the family without first ruling out long QT syndrome (with a long-time electrocardiogram recording). It is of utmost importance that the family keep the drug securely under lock and key and that a dosage of 25–50 mg, taken 1 h before bedtime, is not exceeded. Side effects (mostly mood changes, which can be bothersome) are common during the first weeks of therapy but often recede without dosage adjustment. The anti-enuretic effect, if any, is evident within 1 month. If the effect is partial, desmopressin may be added to the therapeutic regimen. It is important to take regular drug holidays to decrease the risk of developing tolerance. One strategy is to take 2 weeks off medication every 3 months, but some children need to do this more frequently.

Finally, it is important to remember that the enuresis alarm can, and should, be used again in children who are therapy resistant or who need continuous medication to stay dry. The fact that the alarm did not work 2 years previously does not mean that it will not work this time. Likewise, a new desmopressin trial in a previous nonresponder may also be warranted.

Questions (Answers appear following the reference list)

1. Should a 5-year-old child be actively treated for enuresis?
   a Yes, enuresis is a socially handicapping condition and should be treated early
   b Usually not, but this depends on whether he/she is bothered by the bedwetting or not
   c Yes, enuresis is defined as bedwetting in a child 5 years old or more
   d Yes, but treatment should start with desmopressin, since the child is probably too young to be motivated for alarm therapy
2. Why should imipramine not be a first-line therapy of enuresis?
   a We have insufficient evidence that it works
   b It is not curative
   c It is dangerous if overdosed
   d Enuresis is not a psychiatric disorder and should thus not be treated with antidepressants
3. Why is the enuresis alarm recommended as a first-line therapy in enuresis?
   a It is cheap
   b It is curative
   c It is evidence-based
   d All of the above
   e It is easy to use
4. Which of the following factors is *not* implicated by modern research as crucial in the pathogenesis of enuresis?
   a Uninhibited micturition reflex
   b Brainstem malfunction
   c Nocturnal polyuria
   d Neurosis
   e Upper airway obstruction

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Answers to questions

1. B
2. C
3. D
4. D