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The Evaluation and Treatment of Therapy-Resistant Enuresis: A Review

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ABSTRACT

Children with enuresis that neither responds to the alarm or to desmopressin medication usually have nocturnal detrusor over-activity combined with high arousal thresholds as a cause for their bedwetting.

The evaluation of these children is focused on 1) excluding underlying pathology such as kidney disease, urinary tract infection or neurogenic bladder, 2) looking for concomitant day-time bladder problems or constipation, and 3) detecting possible reasons for failure of alarm treatment. A bladder diary is essential, but blood tests, radiological examinations or invasive procedures are seldom informative.

The non-pharmacologic treatment of these children consists of eradication of constipation, if present, and the provision of advice regarding sound drinking and toilet habits. Such treatment is essential but not uniformly sufficient by itself.

The first-line pharmacologic treatment of therapy-resistant enuresis is anticholinergic medication, although this is, as yet, not evidence-based. Anticholinergics can be combined with desmopressin for better efficiency. For children failing all these measures there is still a place for tricyclic antidepressant therapy, provided that adequate safety precautions are strictly observed.

BACKGROUND

Nocturnal enuresis is caused by three interacting pathogenetic mechanisms: The bedwetting child usually has high arousal thresholds (1) and in addition either suffers from nocturnal polyuria (2) and/or nocturnal detrusor over-activity (3). In the first case the child wets his or her bed because the nocturnal urine production exceeds the amount the bladder can hold and he or she is not aroused by the sensa-

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tion of bladder distension; we can call this *diuresis-dependent enuresis*. In the second case the child wets his or her bed because of sudden, uninhibited detrusor contractions that fail to result in sufficient arousal; we can label this phenomenon *detrusor-dependent enuresis. There are also children with combined diuresis- and detrusor dependency* (4).

Diuresis-dependent enuresis is usually not combined with overt day-time bladder dysfunction, whereas in detrusor-dependency careful history-taking usually reveals that the child has day-time incontinence, urgency symptoms or concomitant constipation. The link between constipation and bladder problems is often overlooked (5): if the rectum is used as a storage room – as is the case in constipation – it will deform the bladder and lead to detrusor over-activity and/or residual urine.

The first-line treatment of enuresis without daytime incontinence is the enuresis alarm or desmopressin (6). Children with diuresis-dependent enuresis usually respond to desmopressin (7), which is logical, given the drug's antidiuretic action, whereas the factors that determine whether alarm treatment will work or not are related primarily to the motivation and ability of the family and child to follow the instructions given by the care-giver, and partly also to the degree of arousal disturbance.

This review will focus on the evaluation and treatment of children with therapy-resistant enuresis. "Therapy-resistant enuresis" will in this text denote enuresis that has responded neither to the alarm nor to desmopressin treatment. From the arguments above it should be clear that these children usually have detrusor-dependent enuresis. It is also known that, although the old notion of enuresis as a primarily psychiatric disorder has not stood the test of time, neuropsychiatrical disturbances, such as attention deficit hyperactivity disorder, are overrepresented among enuretic children (8). Since these children often have difficulties in complying with the alarm treatment they tend to be overrepresented in the group of therapy-resistant children as well.

EVALUATION

Patient history

A detailed bladder- and bowel-oriented anamnesis is of paramount importance in these children. Signs such as day-time incontinence (present or previous), urgency or a tendency to either void very frequently or postpone micturition as long as possible should be specifically asked for. Children with urinary tract infections (UTIs) or recurrent bacteriuria often suffer from detrusor over-activity or have residual urine. Likewise, signs of constipation, such as recurrent stomach pains, infrequent bowel movements, encopresis (hard stools) must be looked for.

Underlying kidney disease should be suspected in children with long-standing weight loss, unexplained fatigue or excessive thirst. Neurological explanations can be suspected in children with developmental delay, gait disturbances or recurrent UTIs.

Obviously, it is also important to know whether the child wets his or her bed every

night or just occasionally, how difficult he or she is to arouse from sleep at night and if the child has always been a bed-wetter or not. Importantly, we also need to know if the alarm was tried in the correct way (i. e. consistently used without interruption for at least six weeks, the parents helping the child to wake up at the signal). In many cases it is found that the family did not receive adequate information and follow-up during the alarm treatment, and then a new session can often be curative. The presence of heavy snoring or sleep apnoeas should be asked for, since in some cases the removal of upper airway obstruction can result in disappearance of enuresis (9).

We usually ask the child if he or she – not just the parents – regards the bedwetting as a big problem. If that is not the case, then compliance problems may become an issue and the risk for neuropsychiatric co morbidity is greater.

Physical examination

The evaluation should include a routine neurological examination (hyperreflexia? positive Babinski?), inspection of the genitals (phimosis? ectopic ureteral orifice?), inspection of the lower back and palpation of the rectum. During the latter examination sphincter tone can be assessed and the presence of stool in the rectal ampulla – a strong indicator of constipation – be detected.

Bladder diary

All children with therapy-resistant enuresis should be encouraged to complete a bladder diary, documenting voiding frequency, voided volumes and fluid intake for a few days and enuresis/incontinence episodes and bowel movements for two weeks. This gives invaluable information about bladder and bowel function. Frequent, small voiding and urgency indicate day-time detrusor over-activity. Infrequent voidings and holding manoeuvres such as squatting or standing on tip-toe with legs crossed indicate voiding postponement and should prompt behavioural change. Excessive urine production indicates kidney disease or habitual polydipsia. A low defecation frequency obviously gives reason to suspect constipation.

Furthermore, the ability of the child and family to fill in the bladder diary gives a good indication about their ability to comply with treatment requiring a high degree of cooperation, such as urotherapy, bowel therapy or the enuresis alarm.

Other investigations

If the child has previously been dry it is obvious that a urine test for leukocytes, bacteria and glucose should be performed in order to exclude UTI or diabetes mellitus. Blood tests, however, are not informative if the above examinations have not given any suspicion of kidney disease. Neither is ultrasound or x-ray examinations indicated. Cystometry or cystoscopy is only indicated in the rare cases when the history or physical examination gives reason to suspect neurogenic bladder disturbance. In children with heavy snoring or nocturnal apnoeas the help of an otorhinolaryngologist should be sought for sleep registrations and possible surgical correction.

Flowmetry, with assessment of residual urine volume, is a very useful investigation in these children, since it gives valuable urodynamic examination. It is our opinion that it is an obligatory examination at least in children who have additional day-time incontinence that has not responded to basic urotherapy and in enuretic children who have had UTIs. This way, the few children who need to be examined under the suspicion of urethral valves or neurogenic bladder disturbance may be discerned.

CHOICE OF TREATMENT

After the evaluation outlined above we usually have sufficient information to discern which patients need further investigation and be able to start treatment of the remainder. Reasonable strategies for different patient groups are presented below, whereas the different medications are described in more detail in the following section.

Children who have relapsed after successful alarm treatment

These children should be given the alarm once more. If it worked previously it will probably work again. This time the strategy of over-learning may be used (10), i.e. the child is asked to start drinking extra water at bedtime after primary alarm success is achieved and then continue until 14 consecutive dry nights have been achieved in spite of the extra fluid intake.

Enuretic children with concomitant day-time incontinence

The general rule is to treat day-time incontinence before addressing the enuresis, although this has recently been challenged (11). First-line treatment of the former is bladder training, which will be most effective with the help of a skilled urotherapist. Basic urotherapeutic advice that can be given by everyone is that the child should void regularly every second or third hour and that at least half of the day's fluid intake should take place before the afternoon. Constipation, if present, should be treated (see below).

If dysuria or unexplained fever is present a urine culture should be obtained and antibiotic treatment be considered. Note, however, that this needs to be carefully evaluated. If there is no prompt disappearance of symptoms during antibiotic treatment then the bacteria were not causative. Asymptomatic bacteriuria is common in children with bladder problems (12).

If the day-time incontinence remains in spite of bladder training anticholinergic medication may be indicated, given twice or thrice daily or as prolonged release tablets, but before this is considered it has to be ascertained that there is no residual urine present.

When the day-time incontinence has disappeared the enuresis – if still present – should be treated with anticholinergics (see below), provided that the alarm has not been effective.

Enuretic children with suspected detrusor over-activity but without day-time incontinence

The same basic urotherapeutic advice as outlined for the day-time incontinent children should be given, but in our experience this is seldom enough to make the children night-dry. The first-line treatment that we recommend is anticholinergics, given once daily in the evening. Note, however, that this is an experience-based, not evidence-based, recommendation (13). If the response is partial desmopressin may be added.

Enuretic children with constipation

As mentioned above, bladder disturbances and constipation is a very common but often overlooked combination. This is especially the case in children with day-time incontinence or both day- and night-time wetting (14), but constipation may be relevant in quite a few children with isolated enuresis as well.

In these children the constipation should be addressed first. We recommend that treatment is started with daily mini-enemas for 3 or 4 consecutive days, followed by bulk laxatives of the non-irritant type for at least a month. The child is instructed to drink lots of water but not too much milk, go regularly to the toilet at least once daily (preferably after meals), eat plenty of fibre-containing food, keep an active lifestyle (not just sit in front of the computer or TV all day!) and – last but not least – develop the habit of going directly to the toilet upon first sensation of rectal filling. Sometimes the help of an anotherapist is needed to succeed with this treatment.

Constipated children with enuresis can be assumed to have detrusor over-activity as the direct cause for their bedwetting and anticholinergics will then be the logical treatment if the alarm, basic urotherapy and eradication of the constipation by itself have not made the child dry. However, as anticholinergics often cause constipation as a side effect, these children should continue on laxative treatment as long as they use these drugs.

Enuretic children with no sign of day-time bladder or bowel disturbance

It is unclear at the moment if these children are best helped by anticholinergic medication, assuming that they have isolated nocturnal detrusor over activity, given as a monotherapy or combined with desmopressin at bedtime, or if they should be given tricyclic antidepressant medication with imipramine. The former alternative is not evidence-based in enuresis and the latter is actively disencouraged by many authorities (see below).

For this reason we recommend – always provided that first-line therapy has been adequately tested and failed – that even these children are first given anticholinergics (with the addition of desmopressin in the case of partial response), and that we proceed to imipramine only if this fails.

Enuretic children who have not responded to, or not tolerated, anticholinergics

These severely therapy-resistant children deserve the attention of a specialist, usually a paediatric nephrologist or a paediatric urologist with a specific interest and experience of bladder problems.

Blood tests or invasive examinations such as cystometry are usually not indicated even in this group but the bladder diary, uroflowmetry and measurement of residual urine certainly are. Ultrasound of the kidneys and urinary tract should also be considered, looking for bladder wall abnormalities, kidney cysts, ureterocoele etc, although usually nothing abnormal is found.

Since the response to first-line treatment modalities may change as the patient grows we recommend that new attempts with desmopressin and the alarm treatment are performed every second year or so in these patients.

With these considerations taken into account it is our opinion that imipramine should be offered to these children.

ANTICHOLINERGICS IN ENURESIS

Three drugs have been more than sporadically tested in children: oxybutynin, tolterodine and propiverine. The drugs have anticholinergic and smooth muscle relaxant properties. The clinical efficacy is probably equivalent but tolterodine has fewer side effects (15) and is therefore the drug that we most often use in these children.

Anticholinergics are well-established and evidence-based in the treatment of daytime urinary incontinence when urotherapy alone does not suffice (16). Clinical experience indicates that it is also effective in many children with enuresis (4, 17), which is logical, given the overlapping pathogenesis of the two conditions, but, as yet, this has not been proven in randomized, controlled studies. For this reason, we suggest that these drugs only be used by doctors with specific expertise in the field of paediatric bladder disturbances.

Considerations before starting treatment

In children who have had UTIs residual urine has to be excluded. This is also the case when medication during both evening and morning is considered. The presence of a residual of >20 ml or >15% of the voided volume after repeated voiding is a contraindication for anticholinergic treatment.

Constipation should also be ruled out or treated before treatment is started. If the child has recently been constipated bulk laxatives should be given as long as the child takes anticholinergic medications.

Side effects and risks

Anticholinergic drugs are not highly toxic but side effects are fairly common. These are the most prevalent:

1 *Dry mouth*: This is not a big problem for children, but the family should be informed about the increased risk for caries and the importance of good oral hygiene

2 *Nausea and vertigo*: This problem is much more common in the adult or elderly and only seldom leads to children having to discontinue treatment.

3 *Aggressiveness or mood change* occurs in a significant minority of children and

may lead to a need for discontinuation. It is very rare with tolterodine treatment.

4 *Constipation*: this is the major clinical problem, since enuretic and/or incontinent children have a higher risk for constipation from the start. A common symptom of constipation – apart from the ordinary ones such as stomach ache, encopresis – is that an initially good response to the drug is gradually disappearing with an increasing number of wet nights as the weeks and months pass.

5 *Urinary tract infections*: if a child on anticholinergic treatment has a UTI the accumulation of residual urine should always be suspected. Consequently, these children should discontinue the medication, start antibiotic treatment and undergo measurement of residual urine. The anticholinergic medication can not be started again until the residual urine has disappeared (the help of a urotherapist may be needed to achieve this).

Dosage

The dosage in nocturnal enuresis is 5 mg oxybutynin or 1-2 mg tolterodine given at bedtime, the lower dosage given to children below the age of 7-8 years. Our experience is that the dosage of tolterodine, because of its more benign safety profile, can and should often be increased to 4 mg if 2 mg gives only partial response.

If the child has day-time incontinence in addition to his or her enuresis the same dose should be given in the morning as well, after the exclusion of residual urine.

Follow-up

Children who are given anticholinergic treatment should be told that the pills are only half the treatment. Sound regular voiding and drinking habits are just as important and increase the chance that the child can soon manage without medication.

If there is no effect after 1-2 months of treatment medication should be discontinued and alternative treatment be considered. If there is a partial response to the drug then dosage could be increased and/or desmopressin be added in standard dosage. If there is a satisfactory response to treatment without significant side effects, the lowest effective dose should be sought and treatment continued. It is our experience that first attempted drug discontinuation is usually unsuccessful if attempted before approximately 6 months have elapsed. Discontinuation attempts should be gradual (2.5 mg oxybutynin or 0.5 mg tolterodine reduction per week) and repeated at least every 6 months.

Residual urine measurements are recommended after 6 months of treatment in every child who has previously had UTIs or who is given the drug in slow release tablets or twice/thrice per day. As mentioned above, residual urine measurements are mandatory in the case of UTI. Otherwise, routine measurements are not needed.

IMIPRAMINE

The tricyclic antidepressant imipramine has in several placebo-controlled studies shown better effect than placebo against nocturnal enuresis (18-20). This drug was

widely used for this indication during the 60s and 70s and is still so in some parts of the world, but its use has been steeply diminishing since the alarm and desmopressin became established. One additional reason for imipramine not being recommended in enuretic children today is that it is, like all tricyclics, cardiotoxic in high doses, and there have been tragic cases when children have died due to imipramine overdose (21). The drug is, however, safe and reasonably free of side-effects when given in the usual anti enuretic dosage and when not given to children with unstable cardiac arrhytmias (22).

We have recently shown that more than 40% of children with severe, therapy-resistant enuresis become dry when given imipramine in monotherapy and that this proportion increases to two thirds when the drug is combined with desmopressin (23).

The reason for the anti-enuretic effect of imipramine is not completely clear. It appears earlier, and requires lower dosage, than the anti depressive effect (24). The central sympathomimetic/noradrenergic action of imipramine, promoting arousal and inhibiting micturition, is a more likely candidate (18, 25).

Considerations before starting treatment

Imipramine should only be considered when all of the following conditions are fulfilled:

1 All relevant first- and second-line therapies (the alarm, desmopressin, basic urotherapy and anticholinergics) have been unsuccessfully tested or not tolerated.

2 There is no reason to suspect cardiac arrhythmias, i.e. the child has no history of syncope or sudden palpitations and there are no cases of sudden cardiac death or unstable arrhythmias in the family. If there is any doubt regarding this, an ECG should be performed to exclude long QT syndrome.

3 The family is compliant, well informed and knows that the pills should be kept securely locked.

Side effects and risks

Side effects of imipramine given in anti-enuretic dosage occur in approximately 10% of children (23). The most common side effects are slight nausea, sweating or palpitations, but some children may also experience mood changes or anxiety, effects that often lead to discontinuation of the treatment. All side effects can safely be expected to disappear after discontinuation of the drug.

As mentioned above, there are definite risks of severe cardiac side effects, including death, if the drug is overdosed. It is also dangerous to give imipramine to any child with long QT syndrome, but it is very unlikely that this arrhythmia is missed if a proper case history is taken and ECG is performed on wide indications.

Dosage and follow-up

Imipramine is started in a dosage of 25-50 mg at bedtime, the lower dosage for children below the age of 9. The effect is evaluated after one month. If the result is unsatis-

factory desmopressin, in standard dosage, can be added and/or imipramine dosage can be increased to 50 mg. We never exceed 75 mg even in heavy adolescents.

If the child becomes dry on imipramine treatment it is imperative that regular drug-free intervals are provided, to reduce the otherwise high risk of gradually diminishing effect (23). We instruct the family to discontinue medication for at least 14 days every third month, but some children need to have even more frequent drug interruptions. Of course, if the dry nights continue during such a medicine-free interval it should be prolonged until it is clear that the enuresis has returned. In our experience the child usually can manage without imipramine after a year or two.

OTHER THERAPIES AND FUTURE PROSPECTS

Urotherapy is the mainstay of treatment of day-time bladder problems in children, and it is not illogical to assume that it should have some effect in enuresis as well. The few studies that have so far been performed on urotherapy used as monotherapy for this indication have not fulfilled criteria to provide proper evidence-based recommendations (26-28). It is the author's opinion that urotherapy is an essential component in the treatment of therapy-resistant enuretic children but that it is only seldom effective on its own.

As mentioned above, eradication of upper airway obstruction can cure a small group of enuretic children (9). The intriguing findings of Kurol et al, that the application of orthodontic devices to provide maxillary expansion may be helpful, may reflect similar mechanisms (29).

Acupuncture has now shown antienuretic effect in a sufficiently large number of studies that the positive effect can be suspected not to be just coincidence or publication bias (30, 31). Its specific role in the therapeutic arsenale can, however, not yet be delineated.

The potential cardiotoxicity of imipramine makes it a controversial subject and many experts actively disencourages its use. This situation would improve if a non-cardiotoxic drug could be found that is as effective against enuresis as imipramine. We have recently, in an open pilot investigation, found indications that the selective nor adrenaline reuptake inhibitor reboxetine may be such a drug, but this needs to be confirmed in proper, randomized trials before any recommendations whatsoever can be made (32).

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