WORKSHOP M4 — SLEEP VOIDING DISTURBANCES

Chair: Henri Lottmann, Anders Mattiasson

NOCTURIA: STANDARDISATION OF TERMINOLOGY AND TREATMENT ALGORITHM

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Nocturia can refer to variable symptoms and can be related to different conditions. Therefore standardisation of terminology and definition of is important.
The symptom nocturia can refer to micturition at night but can also be used to indicate the subjective idea of an excessive number of voids interrupting the sleep. The symptom nocturia however will be the result of the relation between urinary output and bladder capacity. Therefore a nocturia index based on the relation between volume of urine voided at night and bladder capacity can be used to define the condition nocturia.
The condition nocturia can be the result of an excessive amount of urine produced at night, abnormal lower urinary tract behavior or a combination of both. The definition of nocturia therefore must include information on nocturnal urine production, bladder capacity and nocturnal detrusor activity.
Definition of abnormal nocturnal urine production hence is essential. This can be based on the absolute volume (ml/night) or on the relative value (nocturnal volume as a % of daytime urine volume). Also excessive frequency (number of voids/night) and what is abnormal occurrence (number of nocturnal voids/ period of time) must be taken into account.
Finally we should consider that nocturia can present as a single entity of as part of other lower urinary tract symptoms.
Based on these considerations the International Continence Society recently published a Standardisation Report of Terminology in Nocturia (1). Based on this a diagnostic and therapeutic algorithm was proposed that will be outlined in the workshop.
Reference:

PhEV Van Kerrebroeck, P Abrams, D Chaikin, J Donovan, D Fonda, S Jackson, P Jenum, T Johnson, G Lose, A Mattiasson, G Robertson, J Weiss. The Standardisation Report of Terminology in Nocturia: Report from the Standardisation Sub-committee of the International Continence Society Neurourology and Urodynamics 21:179-183 (2002)

NOCTURIA AND SLEEP

Poul Jennum

Sleep is an essential biological process that is both highly regulated and very complex. Disturbances to the normal pattern of sleep lead to daytime symptoms (fatigue, sleepiness, mood changes), and increased morbidity and mortality.
Nocturia, a very common condition that has many causes, results in sleep fragmentation and a reduced quality of life. Recent evidence suggests that in professionally active individuals, nocturia can lead to activity impairment and reduced productivity at work.
Desmopressin administered orally prolonged the first period of undisturbed sleep in the majority of patients with nocturia due to nocturnal polyuria, by reducing nocturnal production of urine and the need to void. In approximately one-third of patients, desmopressin normalised the duration of sleep duration.
This findings support former studies showing that desmopressin is effective in patients with nocturnal polyuria in reduced nocturnal diuresis and improve sleep. It is currently not known whether sleep pattern improves and to which extend daytime functioning is improved, why further studies are awaited.

NOCTURIA AND NOCTURNAL POLYURIA

Åsa Rembratt

Nocturnal polyuria is defined as an excessive amount of urine produced during night. The condition is multifactorial and should be distinguished from 24-h polyuria.
The excessive nocturnal diuresis can be solute and/or water driven. The solute driven diuresis involves the hormone ANP, atrial natriuretic peptide, while water driven polyuria is connected to the hormone AVP, arginine vasopressin. The prevalence of nocturnal polyuria depends on the definition used and the population studied. Regardless of definition, nocturnal polyuria has been established as a major feature in nocturia.
Several definitions for nocturnal polyuria have been suggested in literature, based on different principles:

- absolute volume, with or without adjustment for co-factors such as night length or bodyweight
- relative volume; the proportion of 24-hour urine excreted during night
- functional overproduction; nocturnal urine volume exceeding functional bladder capacity.

Also the concept of night has been defined in several different ways either using fixed times or patient defined night, i.e. intended sleeping time. In deciding on a cut-off point for nocturnal polyuria, care must be taken to allow for gender and age differences. Elderly produce more urine at night than do younger subjects, with or without nocturia.
Some of the definitions suggested in literature were applied on a patient material of community-dwelling elderly. Nocturnal polyuria was found in 45 to 100% of elderly with 2 or more voids per night and in 28 to 39% of those with one void or less per night. Different definitions chose different subjects.
More research into the pathogenesis of nocturnal polyuria is required in order to evaluate the respective value of the suggested definitions as outcome measures and/or selection tools for treatment.

RELEVANT OUTCOME MEASURES IN NOCTURIA RESEARCH

Anders Mattiasson

Abstract not available

PRIMARY NOCTURNAL ENURESIS: TERMINOLOGY AND STANDARDISATION

Henri Lottmann

Wetting in children can refer to variable symptoms and can be related to different conditions, and many diagnostic labels for syndromes and types of incontinence have been reported in the literature. In order to avoid confusion and to facilitate comparison of investigations of therapy and outcome, the International Children's Continence Society published a report on standardisation and terminology in lower urinary tract dysfunction in children in 1998.
In pediatrics, enuresis is defined as a normal void occurring at an inappropriate or socially unacceptable time or place.
All forms of wetting other than enuresis should be categorised as urinary incontinence i.e. the loss of small amounts of urine, never a complete void.
Children with nocturnal enuresis void in bed while asleep and are generally not aroused by the wetting. The condition is monosymptomatic i.e the child has no day-time symptoms.
The child should have an age and neurological maturity that suggest that he or she should be dry. From early infancy on, there is a gradual evolution in nocturnal continence. At 5 years of age the child is normally able to start micturition at will and thus developed cognitive control over voiding. Also, the definition of enuresis implies social unacceptability, and rarely the condition is distressing to children under the age of 5 years.
In clinical practice, parental and child concern over the bedwetting, rather than frequency itself, seems the relevant issue. A frequency between 1 – 3 nights per week is a threshold for most parents to seek help. Generally, nocturnal enuresis is not considered a clinical problem when the number of wet nights is less than 1 per month. However, teenagers may find one wet night per month unacceptable.
Several subtypes of nocturnal enuresis have been defined. The traditonal subtypes are based on the child's history of enuresis.

- *Primary Nocturnal Enuresis (PNE).* Monosymptomatic bedwetting in individuals who never have been dry at night for an uninterrupted period of at least 6 months.
- *Secondary or onset nocturnal enuresis.* Monosymptomatic bedwetting in individuals who have been dry at night for an uninterrupted period of 6 months or more.

Secondary nocturnal enuresis appears to be associated with a higher incidence of stressful events particularly parental separation, disharmony between parents, birth of a sibling, early separation of the child from parents and psychiatric disturbance in a parent.
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1. Standardisation and definitions in lower urinary tract dysfunction in children. Nørgaard JP, Van Gool JD, Hjälmås K, Djurhuus JC, Hellström A-L. BJU 1998, 81, Suppl. 3, 1 – 16.
2. Incontinence: Proceedings of the 1st International Consultation on Incontinence, 1998. Conservative Management in Children. Van Gool JD, Butler RJ, Djurhuus JC, Hjälmås K, De Jong TPVM, Kapaln WE, Peters CA, Podesta ML.

PNE: A PLEA AGAINST THE WAIT AND SEE ATTITUDE

Henri Lottmann

In most European countries, primary nocturnal enuresis (PNE) is not considered as a disease particularly by the medical world; as a consequence, there is no specific education at medical school, and a poor involvement from the practitioners. Recently, a survey was conducted in France among 3803 school children (age 5 to 10 years)(ref.1); a questionnaire was also addressed to the mothers of the enuretic children, to 100 school teachers and to 100 school doctors. The prevalence of primary nocturnal enuresis was found to be 9.2 % and 40% of the enuretic children had one or more episode per week. The children declared that bedwetting both-

ered them a lot in a similar percentage (fig.1) as it affected their social life and a majority considered that a doctor could help them (fig 2). Most mothers of enuretic children had a rather tolerant attitude and only a minority proposed to seek for a treatment. However, nearly two thirds of the mothers of children with moderate to severe PNE had consulted a doctor, mainly a general practitioner or a paediatrician. Most of them proposed no solution or a "wait and see attitude"; when a treatment was proposed, it was rather a drug than an alarm (fig 3) and mainly oxybutinin although it is not recommended for the treatment of PNE by the drug company. Finally, most mothers declared that most doctors do not pay enough attention to bedwetting; also a majority of school doctors and school teachers considered that nocturnal enuresis could have negative consequences for the children, affect their social life and that more attention should be paid to the problem. Thus from this survey, it appeared that primary nocturnal enuresis is a concern for children with moderate to severe enuresis, their mothers, most school teachers and school doctors, but it is not a concern for most practitioners who adopt a totally ineffective " Wait and see attitude". This fact is not particular to France but is encountered in most European countries, as reflected by several other surveys, with the exception of Scandinavia.
In 1999, a group of European experts intended to reach a consensus about the way primary nocturnal enuresis should be managed, and these recommendations have been published (ref.2). More recently this group has been extended to an international panel which met in Budapest in April 2002 to update these guidelines. The task of this group will be to define from a meta-analysis of the literature and the opinions of the experts how a patient with PNE should be investigated and treated. If there is a real agreement amongst experts at a European and international level no such consensus exists at a national level at this moment and often opinions expressed by the experts vary a lot from one to another, thus increasing the confusion for the general practitioners. As a consequence, there is a reluctance from the patients or their parents to address the problem of PNE to their doctors; there is also a heavy reliance from the non specialist practitioners about a non-drug treatment and a "wait and see approach to PNE. From these observations the need seems obvious to make of PNE a well defined pathology, to standardise therapeutic approaches and to teach them at medical schools. Ultimately, Enuresis clinics as they already exist in Scandinavia should be promoted.
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2. Nocturnal enuresis: a suggestion for a European treatment strategy. Läckgren G, Hjalmas K, Van Gool JD, Von Gontard A, De Gennaro M, Lottmann HB, Terho P. Acta Paediatrica, 1999 ; 88 : 679-90

PATHOGENETIC ASPECTS OF PNE IN CHILDREN AND ADULTS

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A fundamental concept in modern enuresis research is a differential approach that is based on the fact that nocturnal enuresis is a heterogeneous entity, which can be caused by one or more of several pathophysiological mechanisms that furthermore can result in a phenotype with varying severity and degree of associated symptoms. It is becoming evident that even so-called 'monosymptomatic' nocturnal enuresis (MNE) constitutes a heterogeneous group with one subgroup having a large nocturnal urine production and another a small functional bladder capacity (FBC) as the predominant underlying cause. A unifying concept, however, is that nocturnal enuresis is caused by a mismatch between the nocturnal urine production and functional bladder capacity together with an inability to awaken when this occurs.
An increasing number of studies have substantiated that a large nocturnal urine output is an important pathophysiological factor in MNE, both in children and adults. This has been documented both by thorough inpatient circadian studies and by home recordings of nocturnal urine production using diaper weighing. Furthermore, it was recently shown that nocturnal urine volume is significantly larger on wet nights compared with dry nights which has emphasized that nocturnal polyuria should only be evaluated during nights where enuresis is occurring. The scope of many current research programmes is directed towards the mechanisms behind the increased nocturnal urine output in MNE, e.g. deficient nocturnal vasopressin secretion, nocturnal natriuresis, hypercalcuria, and abnormal aquaporin function. Consistent with these findings is the strong correlation between nocturnal polyuria and a positive treatment response to the vasopressin analogue desmopressin.
Another important factor in PNE is nocturnal bladder capacity. The function of the bladder in MNE has been in focus for many years but the type, prevalence, and clinical importance of bladder dysfunction is still unclear. Although the incidence of significant anatomical and functional bladder abnormalities is very low in PNE it seems that adult onset nocturnal enuresis is a sign of underlying abnormality that demands urological investigation. In MNE most evidence points towards a deficient bladder reservoir function at least in a subgroup and the functional bladder capacity is also a crucial variable when selecting treatment modality. Thus, patients with reduced FBC generally respond poorly to desmopressin but respond well to the alarm treatment.
We are still left with a significant controversy regarding PNE and sleep: the inability to convincingly show abnormalities in sleep patterns or arousability in enuretic children against the fact that these children do not

wake up when the bladder capacity is exceeded and the fact that many parents still have the impression that their enuretic children are deep sleepers. This area of enuresis research still deserves future attention. One area of enuresis research that has progressed impressively over the last decade is our understanding of the hereditary background of the condition. In many families the condition is inherited as an autosomal dominant trait and a number of chromosomal markers have now been linked to the enuresis phenotype. One might have hoped that there would be an association between heredity and various clinical subgroups such as desmopressin responders/non-responders, but such an association has not yet been confirmed. The ultimate goal of identifying specific genes that can cause nocturnal enuresis is definitely within reach and will likely offer valuable information about enuresis pathophysiology.

In conclusion, nocturnal enuresis constitutes a heterogeneous group with some children having a large nocturnal urine production and others a small functional bladder capacity. There is now sufficient evidence to support that for many if not all treatment modalities the treatment response is dependent upon the underlying pathology. It is therefore advisable to include relatively simple procedures to identify such mechanisms, e.g. a reduced functional bladder capacity (voiding diary) and/or an increased nocturnal urine production on wet nights (diaper weighing) before selecting therapy.

PRIMARY NOCTURNAL ENURESIS: TREATMENT ASPECTS

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DEFINITIONS

Primary nocturnal enuresis (PNE) – the child has not been dry for any period of at least 6 months.

Monosymptomatic nocturnal enuresis – the bedwetting is the child's *only symptom*. A *careful history* is needed to establish this fact. It is important to identify the bedwetting as monosymptomatic since nocturnal polyuria (= urinary output during sleep is equal to or more than the output during daytime) plays an important role here, meaning that most of monosymptomatic children respond well to antidiuretic therapy with desmopressin. On the other side, non-monosymptomatic NE with symptoms suggesting a small overactive bladder will need *pretreatment with urotherapy,* often supplemented with anticholinergics.

WHY TREAT?

Two aspects. One, that nocturnal enuresis (NE) is a burden for many children, in particular affecting their self-esteem; and that successful treatment restores their psychological status to the normal range. Two, that active treatment of NE in early childhood may reduce the number of adult individuals with enuresis (around 1% of the population).

WHEN SHOULD TREATMENT BE STARTED?

The child's motivation to receive treatment is the key factor because the child is the one who has to perform the therapy which often has to continue for a long time, months or even years. Some children are highly motivated to get rid of their enuresis already at age 5, while there are 7-year-old enuretics who are still not much concerned about their bedwetting, thus not yet ready to be treated.

THE FIRST CONSULTATION

Ideally, the family should bring a filled-in frequency/voiding chart (F/V chart) at the first consultation. The F/V chart will have surveyed the number of voidings and the voided volumes, and the number of wet nights, during (at least) two weeks. The form for the frequency/volume chart should be mailed to the parents when they make the appointment.

As always, treatment has to be preceded by a careful history and physical examination.

The history should elucidate the child's motivation, possible psychopathology (such as ADHD), suspicion of constipation with fecal retention, symptoms suggesting overactive bladder such as urinary incontinence during the day or deviant micturition pattern (number of daily micturitions 3 or less, alternatively 8 or more), and possible excessive fluid intake during the late hours of the day.

The examination

Besides regular physical exam, feet, legs and the lumbosacral area should be inspected to rule out signs pointing to a spinal cord malformation and rectal palpation should be performed (anal sphincter tonus, fecal impaction in the rectum). Urinary culture and urinalysis (glucose, protein) are the only lab investigations necessary. Measurement of uroflow and residual urine, and cystometry and imaging of kidneys and the urinary tract *are not necessary at this initial stage*

GOOD DOCTORING

includes information, encouragement and instruction to the child regarding simple measures that may in fact cure the bedwetting in a number of children without the use of other measures. The child should be informed that many other children her/his age have the same problem, and that he/she WILL become dry, sooner or later. Instruct the child to drink, eat, void and defecate on a regular basis, and to abstain from drinking too much during the late hours of the day.

Treat constipation
Always before starting specific anti-enuresis treatment!
Urotherapy
If the child has symptoms pointing to bladder dysfunction, *he/she must receive standard urotherapy* (timed voidings) for at least 4 weeks before the start of specific anti-enuresis treatment.
SPECIFIC TREATMENT OF PNE

1. Treatment of NE stands on two strong legs: alarm and desmopressin. Inform the child and the family carefully about the two alternatives (in particular, that alarm requires the parents to take an active part, and that both treatments may have to be used, one after the other or simultaneously).
2. **Prognostic factors for good response**
   Alarm
   Compliant family, small bladder (<65% of volume expected for age, calculated as largest voided volume [ml] = [Age in years + 1] x 30) and *frequent* bedwetting.
   Desmopressin
   Parent(s) unable or unwilling to participate actively in the treatment; true monosymptomatic NE with nocturnal polyuria; and excellent response to small dose of desmopressin (20 µg intranasal or 0.2 mg peroral).
3. Provided that the assessment of the child has not disclosed that one or the other treatment should be preferred (see Prognostic factors), it is up to the child and the family to decide which treatment they want as a start. The family agrees to switch to the other treatment modality if the first one does not lead to a satisfactory response. A *satisfactory response* is defined as a reduction of the number of wet nights (compared to the pre-treatment F/V chart) with at least 50% within 2 months.
4. If the first treatment does not produce satisfactory results within 2 months, the child switches to the other.
5. If the second treatment also yields unsatisfactory results, the child should try *alarm and desmopressin used simultaneously* for a third period.
6. Hereafter, alternating treatment with alarm, desmopressin and the combination will usually lead to dry nights. However, the frustrated child and its family now need a lot of support and encouragement – and the child often needs a “time out” without any treatment.
7. If the response continues to be less than satisfactory for more than 6 months, add anticholinergic medication (or earlier, if there is some suspicion of an overactive bladder, e.g. more than one enuretic episode per wet night).
8. **No success within 1 – 2 years**
   Infravesical obstruction or neurogenic bladder should be suspected, and the child referred to paediatric urology for urodynamics, imaging and endoscopy.
9. **Results of treatment**
   Of children who respond well initially (> 50% reduction of the number of wet nights), about 70% will achieve lasting dryness within 6 months. Initial good response is experienced by 62% of unselected children with monosympto-matic PNE. Thus, only 44% of children with NE can look forward to complete cure within 6 months. *However, all children with enuresis have a chance of becoming dry but may need quite protracted treatment.*

The cure rates cited above apply equally to alarm and desmopressin. Previous studies on alarm treatment have reported much higher rates of cure. However, when the studies were subjected to very careful meta-analysis taking into account drop-outs and relapses, it was found that 45% of alarm treated children wetting 3-7 nights per week achieved dryness during 28 consecutive nights (Jensen IN & Kristensen G, Scand J Urol Nephrol, 2001 and 2002). For children wetting 6-7 nights per week, or every night, the cure rates for alarm were higher.

PSYCHOLOGICAL ASPECTS OF NOCTURNAL ENURESIS

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Epidemiological studies have shown that children with wetting problems are more prone to develop co-morbid psychological problems. One has to differentiate between manifest child psychiatric disturbances of clinical relevance and subclinical symptoms such as sad affect, social withdrawal and lower self-esteem, which can be extremely distressing for children and parents, but are often understandable reactions to the wetting problem and not a disorder per se.
Clinically relevant disorders can be assessed categorically by professional diagnosis according to standardised classification schemes: ICD-10 or DSM-IV; or dimensionally - based on symptom scores by questionnaires with defined cut-offs to delineate a clinical (and sub-clinical) range.
The overall comorbidity of psychiatric disorders and enuresis, in both epidemiological and in clinical studies, are approximately the same: 13.5% - 40.1% of all wetting children have clinical relevant behavioural prob-

lems. The relative risk is 1.3 – 4.5 times higher than in controls or in the general population. One can conclude that approximately 30% of all wetting children show clinically relevant comorbid disorders.
Regarding the specific comorbidity of the different forms of wetting, primary nocturnal enuresis has the lowest rate of psychiatric problems. The subgroup of monosymptomatic PNE is no higher than in the general population (10.0%). The highest rate of co-morbid psychiatric disorders can be found among the secondary nocturnal enuretics (75.0%) (von Gontard et al., 1999).
Regarding the types of problems, externalising disorders predominate: in our own study, 21.0% had an externalising disorder (9.6% a Hyperkinetic syndrome and 11.4% a conduct disorder) and 12.0% an internalising (emotional) disorder (von Gontard et al., 1999). The disorder with a specific comorbidity is ADHD (according to DSM-IV) or the Hyperkinetic Syndrome (according to ICD-10). In our own studies, the rates ranged from 9.3% (HKS) to 13.5% (HKS and ADHD). In a retrospective study, of patients with ADHD, 20.9% wetted at night and 6.5% during the day. The odds-ratios were 2.7 and 4.5 times higher, respectively, which means that there is unspecific association of ADHD and both night/ daytime wetting (Robson et al., 1997).A manifest disorder requires a thorough assessment and specific treatment, as it will not disappear after attaining dryness.
Subclinical behavioural signs and symptoms are common, adequate reactions towards the wetting problem and not disorders. In one study, for example, 35% said that they felt unhappy, 25% even very unhappy about wetting (Morrison et al., 2000). In our own study, 70.3% of children aged 5 to 11 years could clearly indicate that the wetting was of disadvantage (Sonnenschein, 2001). The types of disadvantages or negative consequences were: social ("I can't sleep at friends' house, friends can't stay over night" – in 32.1%), affective ("I feel sad, ashamed, annoyed" – in 16.4%), of isolation ("I feel like a baby, nobody is allowed to know about it, I feel different from other children" – in 6.7%), of sensation ("it feels unpleasant, cold, wet, itchy, nasty" – in 32.1%) or referred to direct consequences ("I have to take a shower, sleep in pampers, won't get a bicycle" – in 17.6%). Only 4.9% reported any advantages of the wetting at all ("I like the wet feeling, get more attention from mother").
One subclinical construct of special importance is that of **self-esteem.** It has been defined as definition: "relatively stable set of self-attitudes reflecting both a description and an evaluation of one's own behaviour and attitudes" and is important attribute thought to be associated with mental health. Although there is no conclusive evidence that bedwetting leads to lower self-esteem, there can be no doubt that self-esteem can improve upon attaining dryness. In one randomised study of alarm treatment versus waiting list, self-esteem increased in the treatment group, increased in children with total success and with > 25% improvement, but showed no increase in children with treatment failure (< 25% success) (Moffat et al. 1987). The study shows clearly that in even children with partial success self-esteem improves – if they are being taking care of.
The effects of "good doctoring" can be seen even more clearly in a second study by the same Canadian centre. In a randomised study, 182 children were treated by alarm, placebo or DDAVP (Longstaffe et al., 2000). The self-esteem scores increased after 6 months – regardless of any improvement. They also increased significantly for the alarm, the DDAVP, but not for placebo group. The authors conclude that „frequent follow-up and emotional support and encouragement appear to be important components of an efficacious intervention for children with nocturnal enuresis".
Conclusion: The rate of clinically relevant behavioural and emotional disorders is increased among children with wetting problems. Externalising problems such as ADHD predominate. Monosymptomatic nocturnal enuresis has the lowest comorbidity. Subclinical symptoms and distress are more common. Self-esteem improves with treatment.

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