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INSIDE

Advancements and Updates in the Field of Enuresis

ADVANCEMENTS AND UPDATES IN THE FIELD OF ENURESIS

Summary of the Enuresis Lecture, held at the 25th Annual ESPU Congress, Innsbruck, Austria, on 9th May 2014

Speaker

Paul F. Austin

Professor, Division of Urology, Washington University in St. Louis, St. Louis Children's Hospital, St. Louis, Missouri, USA

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PRESENTATION SUMMARY

Dr Austin's presentation aimed to provide a state-of-the-art review on enuresis, focusing on diagnosis, treatment strategies, and management of therapy-resistant patients.

Definitions and Epidemiology

Dr Paul Austin began his presentation at the European Society for Paediatric Urology (ESPU) by acknowledging that Europe is a leader in enuresis research, particularly with the development of the small therapeutic peptide, desmopressin, and the numerous genetic studies aiming to explore the pathophysiology of enuresis.

As a starting point, Dr Austin discussed the importance of terminology in describing incontinence disorders and highlighted the new International Children's Continence Society (ICCS) terminology for lower urinary tract (LUT) function in children and adolescents published in the *Journal of Urology*.[1] It is the third standardisation of terminology for LUT function,[2,3] addressing recent developments in research on bladder and bowel function: Dr Austin recommended that physicians familiarise themselves with this specific terminology.

He then reminded the audience that enuresis (or bedwetting) is defined as intermittent incontinence while asleep (at night time or during nap time). This disorder is quite common in children, and is most prevalent in the 5-10-year-old group, occurring in about 15% of 5-year-olds, 9% of 7-year-olds, and 5% of 10-year-olds. It has a slow resolution over time, and only occurs in 1 or 2% of adolescents aged 15 years and over.[4] Enuresis is more prevalent in males than in females, with a 2:1 ratio.[5]

It was explained that the pathophysiological mechanisms of enuresis are still being fully explored but it appears that there is a genetic component to the development of the disorder. Some possible loci have been described on chromosomes 12, 13, and 22, but the exact gene has not yet been found.[6] A child with one parent who had enuresis has a 44% risk of developing it as well, and this risk soars to 77% if both parents wet their beds.[7] Furthermore, in monozygotic or identical twins, there is a 68% concordance rate of incidence of enuresis; in fraternal or non-identical twins, the incidence drops to 36%.[8]

If left untreated, enuresis can persist within adult life, but also has an impact on the child in terms of self-esteem, overall well-being, and psychological health.[9-11] It can also impair socialisation with ramifications towards important events for a child such as summer camp or spending a night at a friend's house.

Diagnosis

It was stated that enuresis can be treated with many different approaches, but first and foremost,

physicians must identify or exclude other underlying causes and dysfunctions that would require other therapy. Dr Austin then described the classic triad of enuresis causes as proposed by Butler et al.,[12] involving three organs: polyuria (kidneys), detrusor overactivity (bladder), and higher arousal thresholds (brain) (Figure 1). If only two of these factors are present, enuresis can occur, but in many patients there is an overlap of these three factors in a variety of presentations, but almost all resulting in refractory disease. Thus, the screening and diagnosis processes are important and must be executed thoroughly.

There are multiple guidelines regarding evaluation strategies, but they all agree on the key concept of determining whether the patient has monosymptomatic nocturnal enuresis (MNE) or non-monosymptomatic nocturnal enuresis (NMNE). It was indicated that the diagnosis of MNE is established in a child without any type of daytime bladder symptoms, as follows: enuresis without urgency, incontinence, increased/decreased voiding frequency, voiding postponement, holding manoeuvres, or interrupted flow. Otherwise, when one or more of these symptoms are present, enuresis is defined as NMNE.

Evaluation strategies have been developed as guidelines by the ICCS and the ESPU; these address both MNE and NMNE.[13-15] Dr Austin highlighted that patient evaluation should follow MNE/NMNE and lower urinary tract dysfunction (LUTD) guidelines. New assessment tools that are emerging were also discussed, such as mobile applications containing bedwetting and/or voiding diaries; these are available in many languages and are useful tools that physicians are going to be using more and more over time.

Treatment Strategies

Dr Austin continued his presentation by providing a short overview of treatment modalities for MNE and NMNE. For isolated bedwetting (MNE), there are two main therapeutic options, namely desmopressin therapy and alarm therapy. The rationale for desmopressin therapy is that it reduces the amount of urine produced by the kidneys, while alarm therapy uses small sensors attached to the child's underwear which set off an alarm when wet to help the child identify the need to go to the toilet.

NMNE accounts for approximately 30% of the total nocturnal enuresis (NE) population[16] and is associated with increased behavioural comorbidities in 20-40% of these cases, often involving externalising behavioural patterns (e.g. attention deficit hyperactivity disorder [ADHD]) over internalising symptoms.[17] These comorbidities should be treated concomitantly to enuresis.

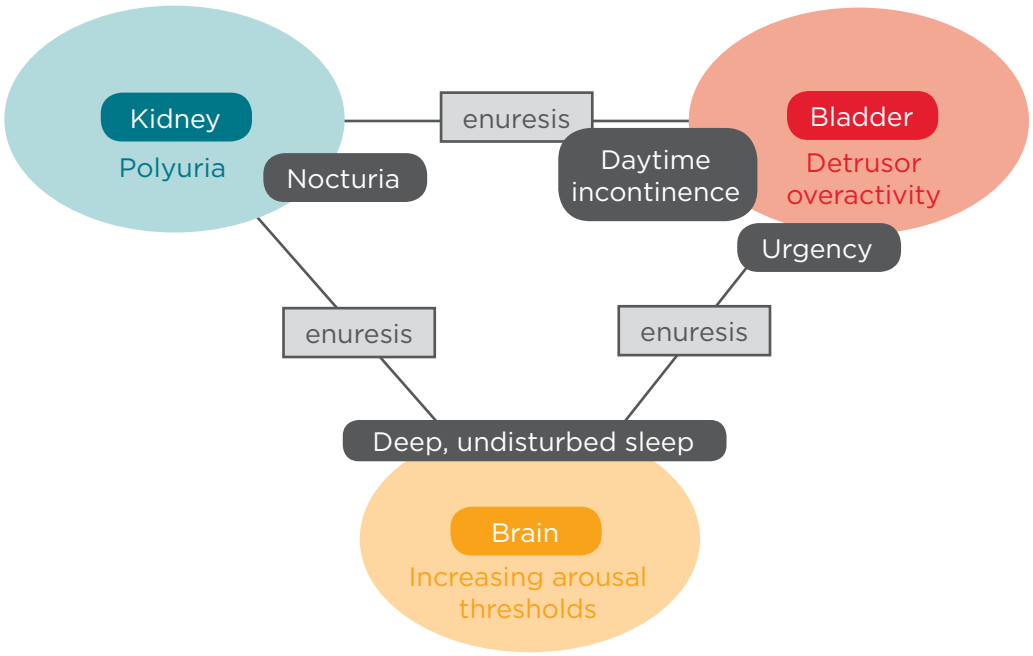

Figure 1: The three systems - the classical triad of enuresis causes.
Adapted from Butler RJ, Holland P.[12]

Moreover, it was stressed that in NMNE, physicians should explore and address bowel symptoms first, then daytime LUTD symptoms, and finally enuresis.

Finally, Dr Austin indicated that management of LUTD includes many treatment modalities reflecting the multifactorial physiopathology of enuresis, such as urotherapy, biofeedback, alarm therapy, bowel therapy, clean intermittent catheterisation, botulinum toxin, centrally active drugs, neuromodulation, and anticholinergics.

Refractory Enuresis

It was explained that enuresis can be refractory to desmopressin or alarm therapy. The common causes of treatment resistance to desmopressin include NMNE where the patient has a severely overactive bladder (OAB) or bladder and bowel dysfunction (BBD), while some patients can present with concurrent reduced maximum voided volume (MVV) and nocturnal polyuria (NP).[18-20] Other causes for refractory enuresis include reduced patient compliance which may occur in about 70% of these patients after 3 months of treatment,[21] renal tubular abnormalities with NP due to sodium excretion,[22,23] excessive increased water intake at night,[24] or reduced bioavailability of some medication formulations (oral lyophilisate versus tablets).[19,25]

Most of the common causes of treatment resistance to alarm therapy overlap with those of desmopressin and include severe OAB or BBD, MVV plus NP,[18,20] and reduced compliance to treatment.[21] But resistance to alarm therapy can also be caused by infrequent enuresis (occurring up to two nights per week, thus not allowing the learning mechanism to be fully efficient and affecting the response rate), co-morbidities (ADHD or obsessive-compulsive disorder), unrecognised sleep disordered breathing, or poor follow-up.

Management of Refractory Enuresis

Dr Austin continued his presentation by discussing the management of therapy-resistant enuresis and stated that, first and foremost, assessment reinforcement or further evaluation with a flow-voiding chart must be conducted. A home registry for 1 or 2 weeks can also be implemented in order to record nocturnal urine volume (by weighing the pads, diapers, and first morning void, with and without desmopressin).

The strategy when facing alarm-resistant enuresis was then discussed. This consists of excluding OAB and reduced bladder capacity with nocturnal polyuria, as well as making sure that there are no compliance-related issues in the child or the family and exploring comorbidities, including psychological issues and sleep disordered breathing. Similarly, Dr Austin explained the management approach for desmopressin-resistant enuresis, which requires the exclusion of any kind of LUTD (OAB, reduced bladder capacity), nephrogenic diabetes insipidus, or compliance-related issues. An exploration of the dietary history can also be useful, particularly salt and water intake, as they can significantly influence nocturnal renal tubular handling of urine production.

Moreover, if the patient suffers from constipation concomitantly with enuresis, the former needs to be treated first. Psychological comorbidities such as ADHD, attention deficit disorder (ADD), or autism need to be referred to and managed by either a psychologist or a psychiatrist.

A few therapeutic options in this clinical setting were then recommended; these included: earlier desmopressin administration (approximately 1 hour prior to bedtime), increased doses, and considerations to switching to the oral lyophilisate formulation, which is associated with a greater bioavailability.

Efficacy of Combination Therapy with Anticholinergic Drugs

Dr Austin then shared a few data points from one of his studies, conducted in 2008, in which desmopressin-resistant MNE patients were randomly assigned to either desmopressin combination therapy with tolterodine (an anticholinergic drug) or a placebo.[26] The response rate, defined by the reduction in mean number of wet nights per week, was significantly higher in the combination group ($p<0.05$; Figure 2). However, a real placebo effect was also observed, as about 34% of enuresis cases from the placebo arm were improved during the study. In a generalised estimating equation analysis aiming to explore the risk of enuresis per night, a decrease of about 66% was observed in the combined therapy treatment group (desmopressin plus anticholinergic) when compared to the placebo group (OR 0.33; 95% CI 0.12-0.98).

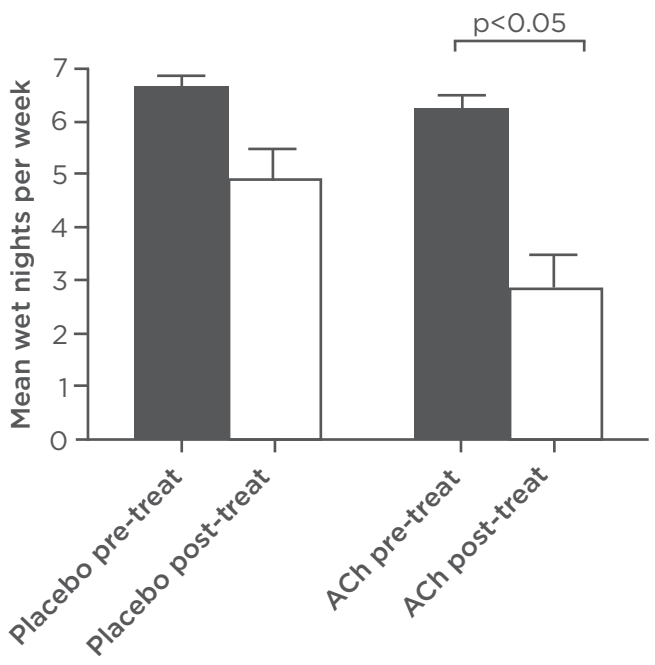

Figure 2: Combination therapy treatment responses; numbers of wet nights before therapy (Pre-treat) and after therapy (Post-treat) (mean ±SE).
Adapted from Austin PF et al.[26]

It was indicated that since this study, more studies have been completed to further explore combination therapy. In a double-blinded randomised clinical trial, the same combination of desmopressin plus tolterodine was evaluated in a larger cohort, and yielded comparable results.[27] Another combination with oxybutynin was also evaluated in a double-blinded, placebo-controlled randomised clinical trial, and demonstrated an improved response for the combination arm.[28] Recent data were published on desmopressin combination therapy with properivine, also revealing significant differences in terms of complete or partial responses and rapidity of response to therapy.[29]

Dr Austin acknowledged that present knowledge does not currently allow physicians to determine if one anticholinergic drug is superior to the others, but the evidence strongly suggests that combination therapy has a beneficial effect over desmopressin monotherapy in therapy-resistant patients.

Towards a Treatment Algorithm?

To sum up the topic of management, an algorithm was described that, as seen for the evaluation process, mainly addresses enuresis by segregating the patients into two categories: NMNE and MNE (Figure 3). In this algorithm, any BBD needs to be treated and every child undergoes behavioural therapy. Treatment modalities need to be tailored to the patient characteristics and the family in order to maximise the chances of treatment success. Depending on the response, the physician may choose to switch over to the other therapies and then try other modalities such as tricyclic antidepressants (e.g. imipramine) and various combinations or other drugs (e.g. indometacin).

The two main strategies to consider in difficult-to-treat patients are: reducing nocturnal output (with desmopressin and/or fluid restriction) and increasing bladder capacity (bladder rehabilitation, increased fluid intake, anticholinergics, or imipramine).

Recent Findings in the Pathophysiology of Enuresis

Dr Austin then presented an overview of recent findings, demonstrating a central involvement in the pathophysiology of enuresis, particularly through sleep quality. Indeed, children with enuresis often have a poorer sleep quality, with lower percentages of motionless sleep and increased periodic limb movements, as demonstrated by the study completed by the Ghent group.[30] Additionally, children with enuresis have shorter periods of continuous sleep and are more tired in the mornings and evenings.[31]

A significant finding by the Aarhus group (Denmark)[32] is consistent with available data on enuretic children; sleep deprivation was explored in healthy children, and results revealed that sleep deprivation increases natriuresis and diuresis. These results strongly support the role of the central nervous system (CNS) in the pathophysiology of enuresis, as recent studies also revealed an important impact of CNS-mediated regulation of bladder control, regarding both efferent and afferent limbs of the bladder, and involving motor and sensory mechanisms.

The role of sleep disordered breathing in enuresis has been previously established;[33,34] however, in patients with obstructive sleep apnoea (OSA), the role of adenotonsillectomy is still uncertain as mixed results were obtained in clinical studies. Approximately 50% of patients became dry following the procedure,[35] and it seems that OSA increased frequent arousal with apnoea episodes.[36]

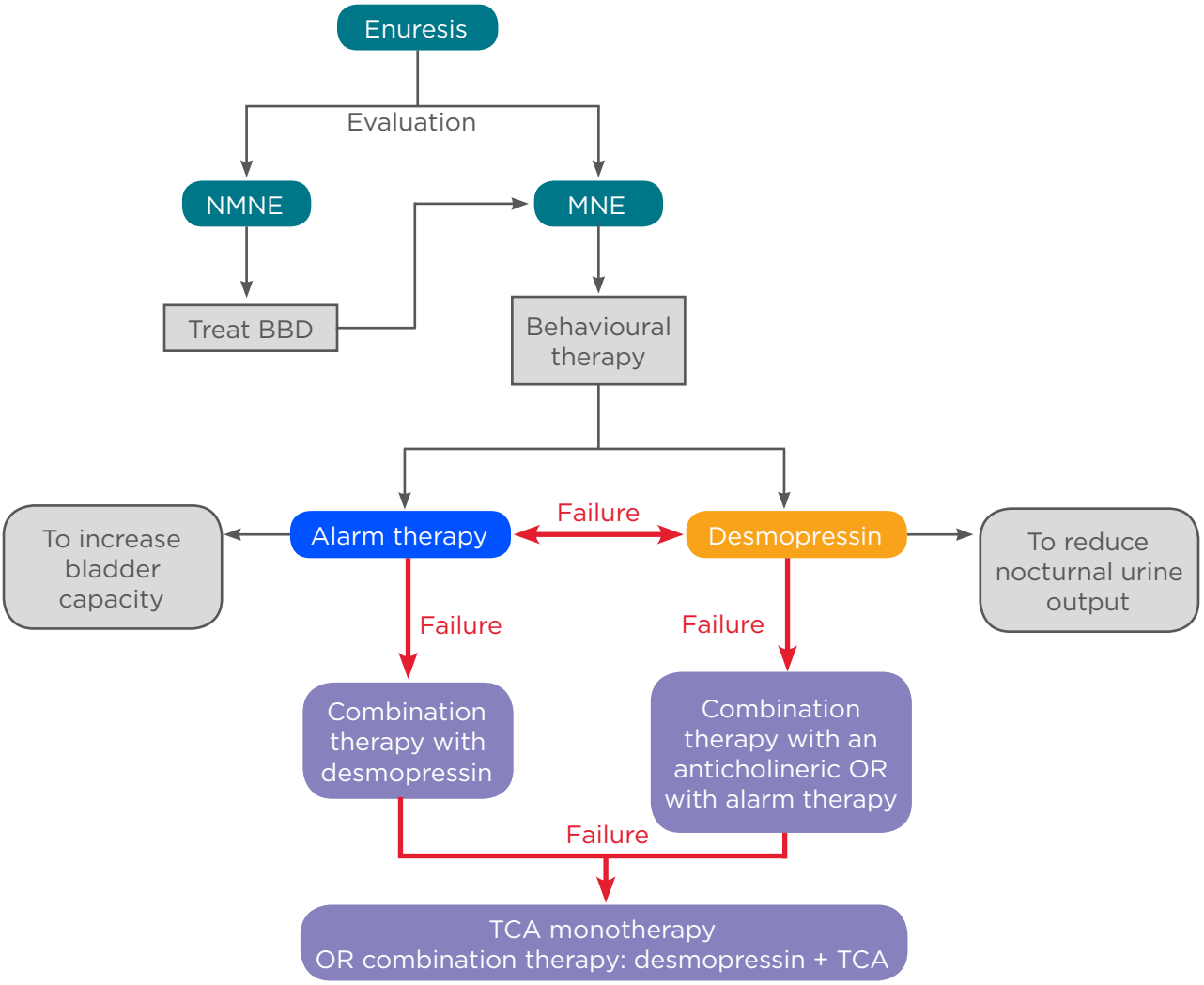

Figure 3: Treatment algorithm for enuresis.
BBD: bladder and bowel dysfunction; MNE: monosymptomatic nocturnal enuresis; NMNE: non-monosymptomatic nocturnal enuresis; TCA: tricyclic antidepressants.

At 36 months follow-up, there was a significant re-emergence of symptoms for sleep-disordered breathing and, interestingly, recurrence of OSA in the long-term seemed to be correlated with body mass index, apnoea-hypoxia index, and enuresis.[37] Dr Austin reminded the audience that it is important to consider the long-term effects of this surgery as the relapse rate is still high, while further evaluation in clinical studies will help with determining appropriate strategies.

Prof Eggert's group[38] exploration of CNS pathways in numerous prepulse inhibition (PPI) studies, using the startle reflex as a barometer of lower brainstem reflex control, was also mentioned. Key findings revealed different PPIs in healthy versus enuretic children and in NMNE versus MNE. Additionally, it seems that PPIs can be altered with alarm or desmopressin treatment, highlighting their fundamental role in enuresis pathophysiology.[39]

The interesting relationships between enuresis and sexual factors were then cited; ejaculation is regulated by the spinal control centre (spinal ejaculation generator) that is influenced by supraspinal sites (above the brainstem, hypothalamus, and preoptic area) similar to supraspinal regulation of the pontine micturition centre. Consequently, there is a higher historical prevalence of MNE in men with lifelong premature ejaculation (i.e. systematic, not acquired) and shorter intravaginal ejaculation latency time.[40,41]

Dr Austin concluded his presentation by enunciating the topics and underexplored areas that are very promising in enuresis research, such as molecular pathways and genetic profiling

with microarray and epigenetics, genomics, and proteomics. Expanding the knowledge on the pathophysiological mechanisms of enuresis will certainly help refine the management of enuresis, a disorder that is considered as benign but is nonetheless quite complex.

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