NEW INSIGHTS IN NOCTURNAL ENURESIS: GOING DIGITAL, SLEEP, AND GENETICS

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Chairperson

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MEETING SUMMARY

Prof Tekgül opened this symposium on nocturnal enuresis (NE). Prof Bogaert described new digital initiatives for engaging with children, parents, and physicians, which included a description of the Drydawn app and reference to the Bedwetting Resource Centre (BRC). Prof Vande Walle discussed recent studies in bedwetting, demonstrating that children with nocturnal polyuria (NP) are not simply deep sleepers. The meeting concluded with a summary of recent advances in the genetics and treatment of NP by Prof Rittig.

Introduction

Professor Serdar Tekgül

Prof Tekgül welcomed the audience to the Ferring-sponsored satellite symposium on NE.

Bedwetting Going Digital – Drydawn App?

Professor Guy Bogaert

The inaugural World Bedwetting Day, a collaborative initiative between the International Children's Continence Society (ICCS) and the European Society of Paediatric Urology (ESPU),

took place on 17th October 2015. World Bedwetting Day 2015's slogan, 'Time to Take Action', recognises that much more can be done to diagnose and treat children who suffer from bedwetting. A key theme of World Bedwetting Day is engagement through digital channels with the children themselves, parents, and other caregivers such as teachers and healthcare professionals (HCPs). Bedwetting is still a highly stigmatised medical condition, which is distressing for children and their families. Furthermore, there is a paucity of primary care education on the subject of enuresis, and the ICCS and ESPU have identified a need to provide a single, high-quality repository of internet-based information, a unified voice, and a platform to facilitate cooperation between stakeholders Drydawn.com, the Drydawn app, and the BRC are central to this digital initiative. These digital resources have three main goals: 1) to provide reassurance, education, and advice; 2) to engage with children who suffer from bedwetting, in a fun yet discreet manner, and 3) to help HCPs make an informed diagnosis, particularly those in primary care.

Drydawn.com revolves around a central character called Ingolf, who suffered from bedwetting in the past but has been cured. Ingolf is used as a device to communicate with children and provide information to them and their carers. The drydawn.com website features easy-to-understand tips, advice, and background information about bedwetting (Figure 1).

Many activities can be completed by children alone, whilst others are designed for parents or carers to work through with the child. There are a number of downloadable resources, including diaries, mood meters, and checklists. The video section includes a number of specially designed videos for children and there is a list of 'frequently asked questions'.

The Drydawn app was created to engage with children and motivate them to record information that is useful for carers and HCPs. It was important that the app did not include the word bedwetting in its name, was fun but not childish, and was easy to use. The Drydawn app includes a simple interface for recording the number of 'wet' and 'dry' nights to enable the HCP to monitor bedwetting. The system encourages children to record data by rewarding them with items that can be used to personalise the character Ingolf. With each entry the child is rewarded with a medal that can be exchanged for an item of clothing to dress Ingolf.

Figure 1: The drydawn.com homepage showing Ingolf, his parents, and his doctor.

The app also includes a more detailed diary feature, which records fluid intake and output by monitoring drinking volume and urine output by weighing nappies. As these data are more complex, children may require help from an adult to input the information but medals are still awarded for completing entries. All the information entered into the app will allow the HCP to receive emailed or printed reports containing the child's expected bladder capacity, the maximum voided volume, fluid intake up to 18:00 hrs and over a 24-hour period, and calculation of the average nightly urine production. The report also includes general 'rules of thumb' to assist the HCP in interpreting the data. The app is currently being beta tested and will be initially released in English, with French, Dutch, Danish, and other language versions planned.

Information for HCPs is hosted on the BRC in conjunction with Elsevier (http://bedwetting.elsevierresource.com). Each month, the BRC provides a convenient round-up of relevant articles published in the field. Each article is placed into a specific category for convenience and is accompanied by a brief editorial highlight. In addition to this, the BRC hosts a number of useful tools, such as the Clinical Management Tool for the Diagnosis and Treatment of Nocturnal Enuresis.[1] The BRC also features a number of video presentations and interviews with key opinion leaders.

The next generation of bedwetting information (Drydawn.com, the Drydawn app, and the BRC) will facilitate better compliance, better information exchange, and better communication, leading to more motivated children, which is crucial to bringing us closer to the goal of more 'dry nights' for children.

Recent Sleep Studies in Bedwetting

Professor Johan Vande Walle

Until very recently, NE was considered 'normal' in childhood and the affected children were simply viewed as deep sleepers with abnormal arousal, although early studies failed to demonstrate electroencephalogram abnormalities during deep sleep.[2] Historically, abnormal arousal was inferred from questionnaire data[3] and demonstrated in a study of enuretic boys.[4]

Current evidence for abnormal arousal thresholds is unclear. However, an abnormal circadian rhythm is certainly involved, as are the bladder, kidney, and psychological factors. There is a clear association between attention deficit and NE, with evidence for subjective[5] and objective[4] increases in arousal thresholds. The idea that nocturia is normal in children stems from the adult viewpoint that most clinicians hold: namely that waking up to urinate is normal. However, it is becoming apparent that, unlike adults, children do not wake up to become continent but start to wake up if they are incontinent. This phenomenon is related to the maturation of melatonin, which reaches a peak at the age of 10 years and begins to decrease from the age of 25 years.

The first studies to suggest that children with NE had disrupted sleep were performed in patients with overactive bladders[6] and could not be generalised to monosymptomatic enuresis. A subsequent study of refractory monosymptomatic enuresis in a group of 15 desmopressin-resistant and 14 desmopressin-dependent children showed that 28 of the 29 children had abnormal sleep architecture.[7] These children had a high incidence of 'restless legs' symptoms and their periodic limb movement score (PLMS) index was >5. A follow-up study in an extreme–refractory population demonstrated that PLMS and arousal indices were significantly higher in children with NE than those with other sleep disorders without NE.[8] The above studies suggest that NP, enuresis, sleep disorders, and attention deficit are comorbid conditions. However, they may also have a causal relationship. To investigate this relationship, a recent prospective study has examined the effect of desmopressin on children with monosymptomatic enuresis and NP.[9] The population consisted of 30 children (6–16 years of age) assessed before and after 6 months of desmopressin treatment. Data were gathered on a number of measures, including sleep quality, renal function, circadian rhythm of diuresis, and a range of psychological tests. Psychological tests were administered using questionnaires completed by the child and their parents and teachers. Significant improvements were seen in a number of domains, as shown in Table 1.

Effective treatment of NP leads to improvement in enuresis, sleep quality, and increased daytime cognitive function, suggesting that NP is the underlying cause of enuresis, disturbed sleep, and attention deficit in these patients.

In conclusion, NP is not a benign disorder, and there is mounting evidence which suggests that it causes sleep disruption and cognitive dysfunction.

Table 1: Results of psychological tests following 6 months of desmopressin treatment.[9]

Test result		p value	Respondent
Reduced	Attention problems	p<0.01	Parents
	Internalising problems	p<0.05	Parents
	Externalising problems	p<0.01 p<0.05	Parents Teacher
Improved	Quality of life	p<0.01	Child, parents
	Executive functioning	p<0.05–<0.01	Child, parents, teacher
	Auditory memory	p<0.01	Child

Desmopressin melt is an effective treatment for NP and enuresis, which therefore reduces sleep disruption and leads to improvements in both cognitive function and quality of life. A 'wait and see' approach to NE is no longer appropriate; NP should be taken seriously, and children and their families should be offered treatment.

Nocturnal Enuresis – From Genes to Treatment of Nocturnal Polyuria

Professor Søren Rittig

Twenty years ago, the third International Children's Continence Symposium in Sydney marked the beginning of the modern classification of NE (Figure 2).[10] An important distinction was made between those patients who only wet the bed, now known as monosymptomatic, and those who had additional daytime symptoms. It was also apparent that there was a subset of monosymptomatic patients who had an increased urine production (polyuric), and a subset who produced urine in usual amounts and who also failed to respond to desmopressin (non-polyuric). Data from linkage studies provided evidence that further subgroups of these patients could be discerned according to their genetic dispositions. The ICCS concluded that "a differentiated approach to NE is, therefore, essential for a better understanding of the pathogenesis of this disorder and for designing successful treatment strategies."

This article will briefly review the progress that has been made in striving toward a differentiated approach. Studies of night-time urine production in bedwetting children have shown that these children produce more urine on a 'wet night' than on a 'dry night'. Patients with NP have a normal bladder capacity, but produce an abnormally high volume of urine on a 'wet night'. What constitutes abnormally high urine production in NP has been a matter of some debate. NP was defined by the ICCS in 2006 as production of urine that exceeded 130% of the child's expected bladder capacity, giving the formula: Nuvol equals >130% MVV_{age}, where Nuvol represents night-time urine volume and MVV_{age} is the maximum voided volume for that age.[11] A study of bladder volume in 148 children aged between 3 and 15 years who were not experiencing bedwetting determined that the ICCS 2006 definition only applies well to children between the ages of 4 and 7 years.[12] Based on these data, a population-based definition of childhood NP was proposed: Nuvol = 20 × (age + 9) mL.[12] This definition has been used to predict desmopressin response,[12] but most research continues to use the ICCS 2006 definition. For comparison, the definition of adult NP is night-time urine production >20% of the total daily output for younger adults, and >33% for older adults. A joint International Continence Society and ICCS working group has been proposed to investigate the plausibility of producing a definition that would accommodate all ages.

Urine production can be simply divided into the amount of water and the amount of osmoles (urine osmolarity) that a person excretes.[13] The amount of water excreted is principally determined by the function of the aquaporins in the distal tubules of the kidneys.[14] The amount of aquaporins is determined by the level of vasopressin.[14] Urine osmolarity is dependent on levels of sodium, potassium, calcium, urine, and many other solutes.[13]

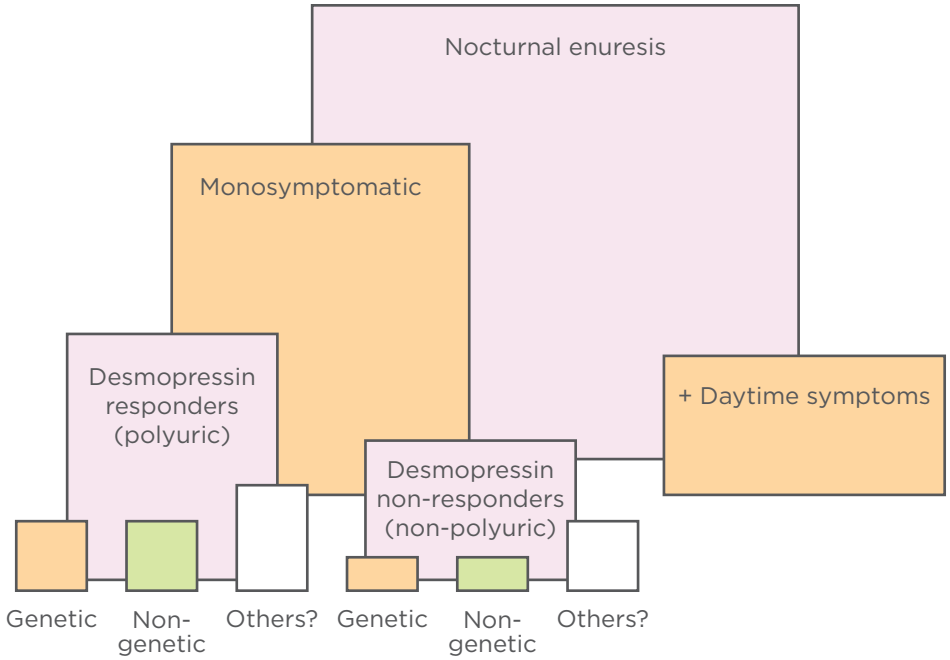

Figure 2: Classification of patients with nocturnal enuresis.[10]

As described above, urine production is only one of a number of factors that contribute to the disturbed sleep seen in NP. The intrinsic circadian rhythm and genetic factors also play a role. PLMS and fragmented sleep may increase blood pressure, which has a direct effect on the kidneys. Renal excretion of sodium and potassium is increased, glomerular filtration rate rises, and vasopressin secretion is suppressed, causing polyuria.

A promising area of research is the discovery of biomarkers that could identify polyuric patients. It would be particularly useful to identify those patients who secrete low amounts of vasopressin, as they are likely to respond to desmopressin. Vasopressin is produced as a preprohormone made up of a signal peptide, large carrier protein, vasopressin itself, and copeptin, a protein of unknown function.[14] Copeptin is a promising biomarker for polyuria because it correlates well with vasopressin levels in the blood and has a longer half-life. The long half-life allows measurement in a morning blood sample, which is far more convenient than measuring urine production.

Our current understanding of the pathophysiology of NP has improved the available treatment options. For instance, we now know that patients who fail to respond to desmopressin have problems with osmotic excretion and a number of treatment options are now available. Indomethacin inhibits prostaglandin production which, in turn, inhibits sodium excretion and potentiates the effects of vasopressin. Imipramine also reduces osmotic excretion. The use of diuretics during the day may deplete sodium levels, thereby preventing increased sodium excretion during the night. Studies are currently ongoing to investigate whether a low-solute diet is an effective treatment in these patients. A promising new development in the treatment of NP is combining one of the above treatment strategies with desmopressin to maximise the effect on urine production.

Advances have been made in elucidating the molecular mechanism of enuresis. Vasopressin attaches to the V2 receptor and activates cyclic adenosine monophosphate (cAMP) production in renal cells. The rise in cAMP stimulates the insertion of aquaporins into the cell membranes of the collecting duct, allowing water to be reabsorbed and subsequently enter the bloodstream. Aquaporin, the V2 receptor, and vasopressin have been sequenced. Linkage analysis has identified five main chromosomal areas of interest: 4p,[15] 8p,[16] 12q,[15] 13q,[17] and 22q,[18] and several candidate genes have been proposed. However, many affected families do not share these markers and so additional loci must be involved.

In conclusion, great progress has been made in our understanding of NP over the last 20 years. Nevertheless, a more robust definition of NP is required. The increasing body of knowledge of the

pathophysiology of NP will provide the basis for personalised treatment. Biomarkers and improved measures of NP will facilitate directed treatments. The genetic basis of NP will soon be determined, and there is hope for a 'dry' future for all children.

Click below to view the following websites:

- **World Bedwetting Day**
- **Drydawn**

REFERENCES

1. Vande Walle J et al. Practical consensus guidelines for the management of enuresis. Eur J Pediatr. 2012;171(6):971-83. Errata. Eur J Pediatr. 2012;171(6):1005; Eur J Pediatr. 2013;172(2):285.

2. Nørgaard JP et al. Nocturnal studies in enuretics. A polygraphic study of sleep-EEG and bladder activity. Scand J Urol Nephrol Suppl. 1989;125:73-8.

3. Nevéus T et al. Depth of sleep and sleep habits among enuretic and incontinent children. Acta Paediatr. 1999;88(7): 748-52.

4. Wolfish NM et al. Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr. 1997;86(4):381-4.

5. Chandra M et al. Prevalence of diurnal voiding symptoms and difficult arousal from sleep in children with nocturnal enuresis. J Urol. 2004;172(1):311-6.

6. Yeung CK et al. Sleep disturbance and bladder dysfunction in enuretic children with treatment failure: fact or fiction? Scand J Urol Nephrol Suppl. 1999;202: 20-3.

7. Dhondt K et al. Abnormal sleep architecture and refractory nocturnal enuresis. J Urol. 2009;182(4 Suppl):1961-5.

8. Dhondt K et al. Sleep fragmentation and increased periodic limb movements are more common in children with nocturnal enuresis. Acta Paediatr. 2014;103(6):e 268-72.

9. Van Herzeele C et al. Desmopressin melt improves sleep and psychological functioning in patients with monosymptomatic nocturnal enuresis. Annual Meeting of the International Continence Society, Rio de Janeiro, Brazil, 20-24 October, 2014.

10. Nevéus T et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176(1):314-24.

11. Rittig S et al. Age related nocturnal urine volume and maximum voided volume in healthy children: reappraisal of International Children's Continence Society definitions. J Urol. 2010;183(4):1561-7.

12. Gwinnutt D, Thorburn J. Body Fluids - Part 1. Anaesthesia Tutorial Of The Week 184. Available at: http://www.aagbi.org/sites/default/files/184-Body-fluids-part-1.pdf. Last Accessed: 30 November 2015.

13. Ikeda M, Matsuzaki T. Regulation of aquaporins by vasopressin in the kidney. Vitam Horm. 2015;98:307-37.

14. Eiberg H et al. Linkage study of a large Danish 4-generation family with urge incontinence and nocturnal enuresis. J Urol. 2001;166(6):2401-3.

15. Eiberg H. Nocturnal enuresis is linked to a specific gene. Scand J Urol Nephrol Suppl. 1995;173:15-6; discussion 17.

16. Eiberg H et al. Assignment of dominant inherited nocturnal enuresis (ENUR1) to chromosome 13q. Nat Genet. 1995;10(3):354-6.

17. Eiberg H. Total genome scan analysis in a single extended family for primary nocturnal enuresis: evidence for a new locus (ENUR3) for primary nocturnal enuresis on chromosome 22q11. Eur Urol. 1998;33 Suppl 3:34-6.