

## Nocturnal Enuresis Treatment: New Perspectives

Juliana Barbosa Goulardins<sup>1,2</sup>, Rita Pavione Rodrigues Pereira<sup>1</sup> and Clarice Tanaka<sup>1\*</sup>

<sup>1</sup>Divisão de Fisioterapia, Instituto Central, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, BR

<sup>2</sup>Biophotonics Applied to Health Sciences, Universidade Nove de Julho, Brazil

\*Corresponding author: Clarice Tanaka, Divisão de Fisioterapia, Instituto Central, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, BR. Dr. Ovídio Pires de Campos, 255 - Cerqueira César, São Paulo – SP, Brazil, Tel: +55 11 2661-3373/6867/7969; E-mail: [cltanaka@usp.br](mailto:cltanaka@usp.br)

Received date: September 15, 2017; Accepted date: October 07, 2017; Published date: October 10, 2017

Copyright: © 2017 Goulardins JB, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Nocturnal enuresis (NE) is a very frequent problem, characterized by involuntary voiding during sleep in individuals aged five years or more, after exclusion of organic causes. This set of associated symptoms may lead to deterioration of bladder function, upper urinary tract and, in extreme cases, even renal failure. The prevalence of voiding dysfunctions is as high as 10% of the world's pediatric population. This commentary discusses the etiology, pathophysiology, and current approaches to therapeutic management of NE. Different studies have shown associations with genetic predisposition, hormonal and metabolic factors, and central nervous system maturation delay. The major pathogenetic mechanisms include nocturnal polyuria, detrusor over activity, and disturbed sleep. Psychologic and behavioral abnormalities seem to be a result, rather than a cause, of NE. We highlight the need for this condition not to be understood as an isolated phenomenon but as a combination of several possible factors in a particular child. Bedwetting is only part of a complex set of changes in children's lives, which leads to important functional impairments and psychosocial disorders, often ignored by the family and even by the health professionals. The scenario of associated disorders demonstrates the need for a comprehensive approach.

**Keywords:** Childhood primary enuresis; Motor coordination; Neural basis

deterioration of bladder function, upper urinary tract and, in extreme cases, and even renal failure [2].

### Introduction

The acquisition of sphincter control is influenced by multiple factors and it is considered a milestone in child development [1]. The age of five years is a marker for lower urinary tract dysfunctions, as this is the age used by international organizations, including the International Children's Continence Society (ICCS) [2], World Health Organization (International Statistical Classification of Diseases and Related Health Problems 10th Revision) [3] and American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) [4] to determine urinary continence or incontinence.

Urinary incontinence is the involuntary loss of urine that can be continuous or intermittent. Continuous incontinence refers to constant losses of urine (day and night); it is usually associated with: (i) congenital malformations, including ectopic ureter, extrophy variant; (ii) dysfunction or loss of external urethral such as sphincter in the external sphincterotomy; and (iii) iatrogenic causes, e.g. vesicovaginal fistula. Intermittent incontinence is the loss of urine in discrete quantities, which occurs while awake, and it is called diurnal incontinence; if the loss occurs exclusively during periods of sleep, it is called enuresis or nocturnal enuresis (NE) [2].

There are four subtypes of NE: (1) primary, with no prolonged dry period; (2) secondary, with the presence of a dry period for at least six consecutive months, but with recurrence symptoms; (3) Monosymptomatic nocturnal enuresis (MNE) with losses only during sleep, and (4) Nonmonosymptomatic nocturnal enuresis (NMNE) with the presence of lower urinary tract symptoms; such as daytime wetting, post-voiding residual, vesicoureteral reflux, urinary tract infection, bacteriuria, etc. This set of associated symptoms may lead to

The prevalence of voiding dysfunctions is as high as 10% of the world's children population. NE is the most common disorder among them. The subtype MNE affects 18.4% of children aged five to seven years; this subtype is more common in boys. However, for the same age interval, the prevalence of NMNE subtype is 16.0% in children, and girls are more affected. Among teenagers, this prevalence decreases up to 4% in boys and 2% in girls. About 15 to 30% of children with NE may also have daytime urinary incontinence. Daytime urinary incontinence is present in 7.8% of children up to seven years of age, with at least two episodes per week, being more common in girls than in boys [5-7].

### Etiology and Pathophysiology

The etiology in NE is not fully understood. The most accepted theory to explain the pathophysiology of NE is based on three conditions: (1) polyuria due to decreased release of vasopressin with increased urine output during the night; (2) bladder instability or detrusor over activity, and; (3) increase in arousal from sleep threshold [6]. However, NE has been reported as a neural development disorder [8,9], and brainstem maturation deficit is considered the possible cause of the dysfunction. However, the developmental delay seems not to be specific for bladder control [10,11]. Niemczyk et al. [12] have reported behavioural changes such as Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), anxiety and depression strongly associated with NE, with a 10.3% prevalence in a study with more than 2000 children.

Recently, research has shown that children with NE present motor performance below expectations for their chronological age. They present deficits in fine and gross motor function, slowing motor

responses in sequential and repetitive movements [13], reduced spatial and visuomotor perception, dysarthria and incoordination [14]. Pavione et al. [15] have found postural misalignments, with anterior pelvic tilt, forward trunk lean, and protrusion of the head. Balance deficits with an increased body sway area in different sensory conditions were found, with worst results in children less than 11 years old compared to teenagers. Motor skills performance, such as balance, posture and coordination, requires both the interaction of neural and musculoskeletal systems and cognitive resources that involve attention and planning [16]. Motor impairment in children with NE may be due to a delay in maturation of central nervous system. Altered cerebellar-thalamus-frontal functional connectivity, including the left and right dorsolateral prefrontal cortex, thalamus, and cerebellar hemisphere, has been demonstrated in enuretic children. These brain areas are linked not only to motor control and cognitive functions, including decision-making, motor planning and movement execution but also to voluntary voiding control. For example, the thalamus whose functions involve motor and sensory signals transmission to the cortex also plays an important role in sleep cycle regulation and relaying sensory afferent information from the bladder [17].

In fact, polysomnography studies have shown alterations in the architecture of sleeping in children with NE [18], characterizing a fragmented sleep. This sleep disturbance generates a state of sleep deprivation and increases the arousal from sleep threshold, which may explain the difficulty response to bladder filling [19-21]. Other sleep disorders have an association with NE, such as apnea [22], snoring [23], parasomnias [24], insomnia [25] and restless legs syndrome. Approximately 50% of children with NE present an episode of tachycardia (and thus an autonomic awakening) before the urination event, in addition to an increase in blood pressure and suppressed plasma levels of all hormones regulating sodium absorption [26,27].

Also, molecular genetic studies have pointed to possible genetic alterations in regions of chromosomes 8, 12, 13 and 22 related to NE [11].

### Traditional Punctual Approach

A diversity of approaches is used in NE conservative treatment, including drug therapy, nocturnal alarms, neuromodulation, standard and specific urotherapy. Some of them are highly recommended by ICCS and all these indications focus on the voiding loss control. For example, the desmopressin which is a synthetic analogue of antidiuretic hormone; or the nocturnal alarm which is composed of a humidity sensor and an alarm clock that wakes the child up as soon as the voiding begins. Physiotherapy plays an important role in the recovery of these individuals. The pelvic floor exercises, biofeedback and the stimulation in the parasacral region are also focused in the voiding effectors' system [28,29].

However, the ideal modality of treatment integrating all the associated conditions, taking into account the neurological development of the child is still missing. All current approaches used do not cover all associated symptoms [18-28], which restrain the proper assessment and treatment of multifactorial conditions, such as presented in NE. Current treatment modalities are conducted in isolation by each professional and directed exclusively for the resolution of urinary symptoms. The emphasis on urinary symptoms is much possibly due to its important social impact, which leads the family to seek professional assistance.

### Conclusion

NE should not be understood as an isolated phenomenon, but rather as a combination of several possible factors in a given child. Bedwetting is only part of a complex set of changes in children's lives, which leads to important functional impairments and psychosocial disorders, often ignored by the family and even by the health professionals.

The scenario of associated disorders demonstrates the need for a comprehensive approach, with multidisciplinary team assistance with all aspects of the child being assessed. Each professional intervention needs to be aligned and discussed in an integrative way, in order to allow the stimulation of general development. The urinary disorder will probably follow the improvement of all the altered aspects of the child.

### References

1. Howe AC, Walker CE (1992) Behavioral management of toilet training, enuresis, and encopresis. *Pediatr Clin North Am* 39: 413-432.
2. Austin PF, Bauer SB, Bower W, Chase J, Franco I, et al. (2016) The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Update Report from the Standardization Committee of the International Children's Continence Society. *Neurourol Urodyn* 35: 471-481.
3. World Health Organization, Geneva (1993) The ICD-10 Classification of Mental and Behavioral Disorders - Clinical description and diagnostic criteria for research.
4. Von Gontard A (2013) The impact of DSM-5 and guidelines for assessment and treatment of elimination disorders. *Eur Child Adolesc Psychiatry* 22: S61.
5. Franco I, von Gontard A, De Gennaro M (2016) Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: A standardization document from the International Children's Continence Society. *J Pediatr Urol* 9: 234-243.
6. Chang SJ, Van Laecke E, Bauer SB, von Gontard A, Bagli D, et al. (2017) Treatment of Daytime Urinary Incontinence: A Standardization Document From the International Children's Continence Society. *Neurourol Urodyn* 36: 43-50.
7. Barbour RF, Borland EM, Boyd MM, Miller A, Oppe TE (1963) Enuresis as a disorder of development. *Br Med J* 2: 787-790
8. Largo RH, Molinari L, von Siebenthal K, Wolfensberger U (1996) Does a profound change in toilet-training affect development of bowel and bladder control? *Dev Med Child Neurol* 38: 1106-1116.
9. Freitag CM, Rohling D, Seifen S, Pukrop R, Von Gontard A (2006) Neurophysiology of nocturnal enuresis: evoked potentials and prepulse inhibition of the startle reflex. *Dev Med Child Neurol* 48: 278-284.
10. Essen J, Peckham C (1976) Nocturnal enuresis in childhood. *Dev Med Child Neurol* 18: 577-589.
11. Von Gontard A, Schaumburg H, Hollmann E, Eiberg H, Rittig S (2001) The genetics of enuresis - a review. *J Urol* 166: 2438.
12. Niemczyk J, Equit M, Braun-Bither K, Klein AM, Von Gontard A (2015) Prevalence of incontinence, attention deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. *Eur Child Adolesc Psychiatry* 24: 837-843.
13. Von Gontard A, Moritz AM, Thome-Granz S, Freitag C (2011) Association of attention deficit and elimination disorders at school entry: a population based study. *J Urol* 186: 2027-2032.
14. Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, et al. (2013) Visuomotor competencies and primary monosymptomatic nocturnal enuresis in prepubertal aged children. *Neuropsychiatr Dis Treat* 9: 921-926.

15. Pavione Rodrigues Pereira R, Nascimento Fagundes S, Surry Lebl A, Azevedo Soster L, Machado MG, et al. (2016) Children with nocturnal enuresis has posture and balance disorders. *J Pediatr Urol* 12: 216.e1-6.
16. Shumway-Cook A, Woollacott M (2010) Desenvolvimento do controle postural. In: Shumway-Cook, A. and Woollacott M. *Controle motor: teoria e aplicações práticas*. (2nd edn). Manole, São Paulo.
17. Yu B, Sun H, Ma H, Peng M, Kong F, et al. (2013) Aberrant Whole-Brain Functional Connectivity and Intelligence Structure in Children with Primary Nocturnal Enuresis. *PLoS ONE* 8: e51924.
18. Bader G, Neveus T, Kruse S, Sillen U (2002) Sleep of primary enuretic children and controls. *Sleep* 25: 579-583.
19. Baert E, Van Herzele C, Raes A, Groen LA, Hoebeke P, et al. (2014) Sleep fragmentation and increased periodic limb movements are more common in children with nocturnal enuresis. *Acta Paediatrica* 103: e268-e272.
20. Cohen-Zrubavel V, Kushnir B, Kushnir J, Sadeh A (2011) Sleep and sleepiness in children with nocturnal enuresis. *Sleep* 34: 191-194.
21. Dhondt K, Raes A, Hoebeke P, Van Laecke E, Van Herzele C, et al. (2009) Abnormal sleep architecture and refractory nocturnal enuresis. *J Urol* 182: 1961-1965.
22. Kovacevic L, Jurewicz M, Dabaja A, Thomas R, Diaz M, et al. (2013) Enuretic children with obstructive sleep apnea syndrome: Should they see otolaryngology first? *J Ped Urol* 9: 145-150.
23. Alexopoulos EI, Kostadima E, Pagonari I, Zintzaras E (2006) Association between primary nocturnal enuresis and habitual snoring in children. *Urology* 68: 406-409.
24. Mason TB, Pack AL (2007) Pediatric parasomnias. *Sleep* 30: 141-151.
25. Mahler B, Kamperis K, Schroeder M, Frokiaer J, Djurhuus JC, et al. (2012) Sleep deprivation induces excess diuresis and natriuresis in healthy children. *Am J Physiol Renal Physiol* 302: 236-243.
26. Kruse A, Mahler B, Rittig S, Djurhuus JC (2009) Increased nocturnal blood pressure in enuretic children with polyuria. *J Urol* 182: 1954-1960.
27. Rittig S, Matthiesen TB, Pedersen EB, Djurhuus JC (1999) Sodium regulating hormones in enuresis. *Scand J Urol Nephrol* 202: 245.
28. Butler RJ, Gasson SL (2005) Enuresis alarm treatment. *Scan J Urol Nephrology* 39: 349-357.
29. O'Flynn N (2011) Nocturnal enuresis in children and young people: NICE clinical guideline. *Br J Gen Pract* 61: 360-362.