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Risk factors and functional abnormalities associated with adult onset secondary nocturnal enuresis in women: a urodynamic viewpoint.

Title page

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Summary:

This study is a review of risk factors and functional abnormalities in women (age ≥ 18) with adult onset secondary nocturnal enuresis

Key words:

Secondary nocturnal enuresis, urodynamics, smoking, antidepressants, stress incontinence, detrusor overactivity

Short title:

Risk factors and urodynamic findings in adult onset secondary nocturnal enuresis in women

Abstract

Introduction

The study describes bothersome lower urinary tract symptoms, risk factors and associated functional abnormalities in women reporting adult onset secondary nocturnal enuresis (SNE), to help understand factors associated with SNE.

Methods

12795 women (age ≥ 18) attending a tertiary referral centre underwent a comprehensive standardized evaluation including urodynamic testing in accordance with International Continence Society recommendations. Records of all patients reporting bedwetting whilst asleep were evaluated under various categories. Multiple logistic regression was fitted to identify statistically significant risk factors and urodynamic findings associated with SNE.

Results

The prevalence of SNE in women undergoing urodynamic testing for bothersome lower urinary tract symptoms was 14.4% (1838). High BMI (OR= 1.47, $p < 0.001$), cigarette smoking (OR= 2, $p < 0.001$), antidepressant usage (OR= 1.8, $p < 0.001$), neurological conditions (OR= 2.12, $p < 0.001$) and previous hysterectomy (OR= 1.19, $p = 0.03$) were significantly associated with SNE. Women with SNE significantly complained of overactive bladder (OAB) symptoms (OR= 1.65, $p < 0.001$) and slightly higher mean nocturia episodes (OR= 1.38, $p < 0.0001$). Low maximum urethral closure pressure (MUCP) (OR= 1.34, $p < 0.0001$) and detrusor overactivity incontinence (DOI) (OR= 1.75, $p < 0.0001$) were significantly associated with SNE. There was no significant association with the symptom of stress urinary incontinence ($p = 0.264$), urodynamical stress incontinence ($p = 0.454$) or detrusor overactivity ($p = 0.231$).

Conclusion

Adult SNE is rarely monosymptomatic and patients usually present with OAB symptoms. SNE is associated with high BMI, cigarette smoking, antidepressant use and neurological conditions. DOI and a low MUCP are possible pathophysiological mechanisms in SNE.

Abstract: 248 words

Key words:

Adult secondary nocturnal enuresis, overactive bladder symptoms, detrusor overactivity incontinence, antidepressants, High BMI

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Conflicts of interest

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Introduction

Nocturnal enuresis (NE) is a highly bothersome lower urinary tract symptom (LUTS) described as involuntary loss of urine which occurs during sleep (Haylen et al. 2010). NE can be considered as primary (life-long) or secondary (arising after a period without bedwetting of at least one year). It can also be monosymptomatic or polysymptomatic (arising in conjunction with other symptoms). NE is common in children and at five years of age up to 25% of children wet the bed (Wan & Greenfield 1997). With each year of maturity the percentage of bed wetting declines by 15 percent. Eight percent of twelve year old boys and four percent of 12 year old girls are enuretic, and this number at adolescence is between one and three percent (Thiedke 2003). Longitudinal follow up studies have suggested that 3% of adults over 20 years of age remain enuretic from childhood and are at risk of remaining enuretic for the rest of their lives (Moilanen et al. 1998; Forsythe & Redmond 1974). However, NE may develop as a new symptom in adults after achieving control for a reasonable period of time (adult onset secondary nocturnal enuresis). Adult onset secondary nocturnal enuresis is the focus of investigation in this paper and will henceforth be referred to as SNE. The prevalence of SNE in women, especially with LUTS, is not known. A large epidemiological survey from the Netherlands suggested an overall prevalence of NE of 0.5% in non-institutionalized adults aged between 18 to 64 years, with no difference in age groups or sexes (Hirasing et al. 2009).

Various mechanisms, including deficient vasopressin release, sleep disorders, psychosocial problems, genetic factors and anatomical bladder problems, have been implicated in the pathophysiology of NE (Thiedke 2003; Hirasing et al. 2009; Yeung 2003; Wolfish 2001; Umlauf & Chasens 2003). A reduction in the bladder capacity has been suggested by some studies (C K Yeung et al. 2002), whilst this is not shown as a significant finding in other studies (Nørgaard & Djurhuus 1993). Detrusor overactivity (bladder instability) has also been implicated in the pathophysiology of NE (C K Yeung et al. 2002; Warwick & Whiteside 1979). NE in men has been suggested as a sign of a high pressure chronic urinary retention due to urethral outflow resistance, with a recommendation for investigations and treatment (SAKAMOTO & BLAIVAS 2001; Abeygunasekera & Goonesinghe 2013). Even though urodynamic investigations have been used in the assessment of adults with NE with or

without other lower urinary tract symptoms, NE is still poorly understood, making management challenging.

This study is a review of findings in all women (≥ 18 years of age) reporting nocturnal enuresis when presenting for urodynamic testing for various LUTS. The study attempts to characterise specific risk factors and urodynamic findings to further our understanding. The aim is to draw conclusions to recommend further research and help manage women with this distressing condition.

Methodology:

The study was registered with the Research and Innovation department, Southmead Hospital, Bristol. Ethical approval was obtained from the regional research ethics committee. All patients were seen in the Department of Urodynamics (Bristol Urological Institute) at Southmead Hospital, Bristol. Patients were referred from local, regional and national centres for urodynamic assessment. All patients were sent an information leaflet regarding the urodynamic procedure along with their appointment letter. A team of doctors and specialist urodynamic nurses saw the patients. Verbal consent was obtained prior to performing the test. A complete history and a pelvic examination were done in all patients. A urine analysis was carried out to rule out any infections in all the patients. Invasive and non-invasive urodynamic tests were done in all the patients according to the recommendations of the International Continence Society (ICS). Frequency volume charts of all the patients who filled them out were analyzed, but only mean daytime frequency and nocturia episodes were entered on to the database. All the patients reporting adult onset bedwetting (SNE) were included in the study. Patients with primary nocturnal enuresis (since childhood), with no period of remission, were excluded from the study. Patients aged less than 18 years were also excluded from this study. Data including history and urodynamic findings were kept on a secure database maintained by the North Bristol NHS Trust, Bristol. All the Trust standard operating procedures and policies were followed in the collection and analysis of the data for this study. Data was analyzed as a whole group and also considered under various associated conditions. NE was also considered in patients with or without overactive bladder symptoms. NE was

also considered in groups according to cigarette smoking, antidepressant use and associated neurological conditions.

Data from the urodynamic database was anonymized and cleaned for clarity, and then analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Student's t-test was used for testing differences in the mean between two continuous variables, while a Chi-square test was used for testing associations between categorical variables. A multiple logistic regression analysis was done with all the covariates in the model to evaluate the risk factors and urodynamic findings associated with SNE. Unless specified otherwise, all tests were made at a 5% level of significance. Whenever appropriate, p-values, Odds ratios and 95% confidence intervals were computed and included in the result.

Results

Data from 12795 women who underwent urodynamics for various LUTS during the study period (January 2000 to December 2010) were reviewed. 1838 women (study group) aged ≥ 18 years complained of secondary nocturnal enuresis in this study, with a prevalence rate of 14.4%. The demographic details of all the patients in the study are summarized in table 1. The average age of women in the study group was 52.6 years (compared to 52.5 in the control group; $p= 0.961$). The mean parity of women with SNE was 2.4, which was the same in the control group. High BMI (≥ 30) was significantly associated with SNE in women (27.4% Vs. 19.4%; OR= 1.47, $p< 0.0001$). A greater proportion of women with SNE also smoked cigarettes (30.1% Vs. 15.9%; OR= 2.03, $p< 0.001$) and reported using anti-depressant medications (16.3% Vs. 8.5%; OR= 1.795, $p< 0.001$). Neurological conditions like cerebro-vascular accidents and multiple sclerosis were significantly higher in women with SNE (10.3% Vs. 5.2%; OR= 2.12, $p< 0.001$). Previous hysterectomy was also significantly associated with SNE (36% Vs. 30.3%; OR= 1.19, $p= 0.032$). Menopausal status was not significantly associated with SNE ($p=0.638$).

Important LUTS and urodynamic findings are summarized in table 2. The mean daytime frequency in women with SNE was 8.3 (SD= 3.4), which was slightly higher compared to 7.95 in the control group (OR= 0.97, $p= 0.03$). The mean

nocturia severity was 1.76 voids per night (SD = 2.8) in women with SNE, compared to 1.26 in the control group, which was statistically highly significant (OR= 1.38, $p < 0.001$). More women with SNE reported overactive bladder (OAB) symptoms (82.6% Vs. 62.6%; OR= 1.65, $p < 0.001$). Prevalence of the symptom of stress incontinence was not significantly different between the groups at history taking ($p = 0.264$).

At uroflowmetry, a higher proportion of women with SNE (8.1% Vs. 7.1%) had post-void residual volume of urine of ≥ 150 ml, (OR = 1.6, $p < 0.001$). The mean residual volume of urine retained in women with significant PVR (> 150 ml) was 325.8 ml compared to 269.1 ml in the control group, which was significant ($p = 0.001$). The average flow rate was slightly less in the SNE group (21.1 ml/s Vs. 21.9 ml/s, $p = 0.017$). Women with SNE had a significantly lower cystometric capacity (219.2 ml Vs. 344.5 ml, $p < 0.001$).

41.1% of women with SNE had low maximum urethral closure pressures compared to 37.9% in the control group, which was statistically significant (OR= 1.34, $p < 0.001$). Detrusor overactivity was seen in 55.8% of the study group (compared to 40.3% in the control) but this was not statistically significant ($p = 0.231$). Detrusor overactivity incontinence was demonstrable in 22.9% of women in the study group (22.9% Vs. 12.4%; OR= 1.75, $p < 0.001$), which was statistically highly significant. Neither a symptom of SUI ($p = 0.264$) nor a urodynamic finding of UDSI ($p = 0.454$) were significantly associated with SNE. A combination of UDSI with DOI (mixed UI) was significantly more prevalent in the SNE group (37.3% Vs. 21.5%; OR= 1.64, $p < 0.001$).

Discussion

SNE is a common condition reported by adult women presenting with bothersome LUTS. SNE is significantly associated with overactive bladder symptoms and urinary incontinence. High BMI, cigarette smoking, antidepressant usage were the most significant risk factors associated with SNE. Neurological conditions and previous hysterectomy were also significantly associated with SNE. Detrusor overactivity incontinence and a low MUCP were the most common associated urodynamic findings.

A prevalence of 14.4% of SNE in women presenting with bothersome LUTS for urodynamic testing suggests a high prevalence of this poorly studied condition. Epidemiological studies in adult populations quote a prevalence rate of around 3% in adult population (Moilanen et al. 1998; Forsythe & Redmond 1974). A large epidemiological survey suggested an overall prevalence of SNE at 0.5% in non-institutionalized adults (18 – 64 years) (Hirasing et al. 2009). A study based on a database review of 3000 patients of adult onset nocturnal enuresis without daytime incontinence quoted a prevalence rate of 0.02% (Schäfer et al. 2002). Our study was based on a large database of adult women who presented with various lower urinary tract symptoms indicating a higher prevalence of SNE in adult women with LUTS. It is an indication of the polysymptomatic nature of the problem. It may also be an indication of how women respond to other LUTS in association with SNE, which also reflects their healthcare seeking behavior.

The majority of SNE patients in our study complained of overactive bladder symptoms (OR= 1.65) and nocturia (OR= 1.38) was a significant association with SNE. SNE is a nighttime problem; it is possible that women get up more often to ensure that they empty their bladder to avoid SNE episodes. Nocturnal polyuria and abnormal diurnal rhythm of plasma vasopressin are suggested as possible mechanisms for NE (Kamperis et al. 2006; Rittig et al. 1989), which could explain this finding. The database however, did not provide data on nighttime voided volumes and hence we were unable to analyze this data further. DO was more prevalent with SNE but this was not statistically significant. DOI (OR= 2.16) was the most significant urodynamic finding demonstrated in women with SNE, which suggests a dysfunction of the bladder detrusor as an important mechanism in the pathophysiology of SNE. Detrusor overactivity has been reported in other studies as one of the predominant urodynamic findings, and an important factor in the pathophysiology of NE (Wadie 2004; Foldspang & Mommsen 1994). A genetic inheritance of SNE with associated DO has also been proposed (Chiozza et al. 1998). Current evidence is conflicting on the role of reduced bladder capacity in the pathophysiology of nocturnal enuresis (Ciftci et al. 2012; Kamperis et al. 2006; Lin et al. 2004). The

mean maximum cystometric capacity was slightly lower in women with SNE in our study (mean difference of 53.3, $p < 0.001$), which does indicate a lower bladder capacity as a possible factor in the pathogenesis of NE. A low MUCP was an independent risk factor associated with SNE and was significantly low in the study group, also suggesting a possible role in the etiopathogenesis of SNE. High maximum urethral closure pressure suggestive of obstruction was not noted in our cases, which is in contrast to some studies suggesting retention with outflow obstruction (C K Yeung et al. 2004). A smaller bladder with detrusor dysfunction and a low MUCP may suggest a possible mechanism of adult bed-wetting. A significant proportion of women with SNE did not complain of stress incontinence, and UDSI was not a significant association, which indicates that stress incontinence is unlikely to have a role in SNE.

Cigarette smoking is associated with overactive bladder symptoms and detrusor overactivity (Tampakoudis et al. 1995; Dallosso et al. 2003). Smoking was a significant finding associated with SNE in our study (OR= 2.26). Nicotine, a nicotinic acetylcholine receptor (nAChRs) agonist, has a role in the modulation of neurotransmitter release in both the central and peripheral nervous systems resulting in detrusor contractile responses (Masuda et al. 2006). It is however difficult to establish a causal role of smoking based on this study. Obesity is a known risk factor for both stress and urgency urinary incontinence (Mayo & Burns 1990; Whiteside & Arnold 1975; Chung Kwong Yeung et al. 2002). Even though the mechanism is not fully understood on its role in UUI, obesity may cause chronic strain, stretching and weakening the muscles, nerves and other pelvic floor structures (Subak et al. 2009). Obesity may also have an effect on nerve conduction velocities, affecting neuronal control of the urinary bladder and contributing to DOI, and in turn SNE (Miscio et al. 2005). Some of these mechanisms may explain the significant association of a high BMI with SNE in the study group.

Even though we have not used any objective tools to measure depression, 16.3% of our patients reported using antidepressants (OR= 2.1, $p < 0.001$). This data could be an indication of a higher association of depression with nocturnal enuresis or may indicate a higher antidepressant usage in women with SNE. It

is difficult to establish a causal relationship based on the data from our study. It is known that NE is associated with depression and low self-esteem in adults (Chung Kwong Yeung et al. 2004). NE might be associated with hypnotic medications (Vural et al. 2007). Antidepressants may also interfere with arousal mechanisms at night, which may lead to nocturnal enuresis (Neveus 2003). Disorders of sleep and arousal have been implicated in the pathophysiology of NE (Umlauf & Chasens 2003; Wolfish 2001). No information could be drawn from the database to evaluate arousal and sleep to explain this finding further.

The integrity of the central nervous system, nervous control of the bladder and the arousal system of the central nervous system are crucial for maintenance of nighttime bladder function (Fowler et al. 2008). A tenth of all our cases with nocturnal enuresis developed secondary nocturnal enuresis in association with a neurological pathology, which indicates a disruption in the neuronal pathways controlling the bladder. Damage to the neuronal circuits, either at the brain or spinal cord, results in unmasking of primitive voiding reflexes and trigger detrusor overactivity and incontinence (de Groat 1997). This may also explain the higher incidence of detrusor overactivity in these cases and explain the associated SNE.

This study is an evaluation of urodynamic findings of individuals complaining of SNE with or without other lower urinary tract symptoms. SNE alone was not the primary focus of the urodynamic testing in many of the cases, but was routinely questioned at history taking. Cystometric tests were done methodologically as per ICS recommendations, which provide valuable data for interpretation and understanding of SNE. All the patients in the study were awake and the test results are an indirect reflection of a problem which occurs when asleep. Urodynamic assessments were conducted when the subjects were awake and hence the findings must be interpreted as only associations. Treatment received and outcomes of treatment were also not available from the database, and some of the cases were referred from other centres for urodynamic testing only. These factors do limit further correlation of the urodynamic findings to patient symptoms and outcomes of treatment. Further long-term longitudinal

studies exploring OAB symptoms and NE are needed to understand symptoms emergence and etiopathogenesis of SNE.

Conclusion

Patients with adult SNE usually present with OAB symptoms. High BMI, cigarette smoking, antidepressant use and neurological conditions are significant risk factors associated with SNE. A low bladder capacity, detrusor overactivity incontinence and low MUCP are the most significant urodynamic findings associated with SNE. Further studies are needed to evaluate the importance of these findings on treatment outcomes of patients with NE.

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Abbreviations used:

NE	Nocturnal enuresis
SNE	Adult onset secondary nocturnal enuresis

DO	Detrusor overactivity
UDSI	Urodynamic stress incontinence
UPP	Urethral pressure profile
OAB	Overactive bladder
BMI	Body mass index
NAD	Nothing abnormal detected
ICS	International continence society
PVR	Post-void residual volume of urine
MUCP	Maximum urethral closure pressure
UUI	Urgency Urinary Incontinence