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Is there a correlation between intravaginal ejaculatory latency time and enuresis? An exploratory study

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Introduction Premature ejaculation (PE) is the most common male sexual dysfunction. Monosymptomatic enuresis (ME) is nocturnal bed wetting, without any daytime symptoms. Recent clinical studies report an association between lifelong PE and ME. The purpose of this study was to compare the intravaginal ejaculatory time (IELT) between lifelong PE in men with and without ME. The goal was to determine if there is an association between the severity of ME and of IELT.

Material and methods A total of 137 men with lifelong PE were included in this study. Subjects were asked if they had childhood ME. The characteristics and mean IELTs of patients with and without ME were compared using the student's t–test, and the correlation between severity of ME and IELT was assessed with trend test.

Results Of the 137 lifelong PE patients, 57 reported ME. There was a strong negative correlation in patients with ME between the severity of enuresis and IELT, with IELT being shorter in patients with severe ME.

Conclusions A strong correlation between IELT and the severity of ME suggests a common underlying mechanism. Further studies are required to confirm these findings and elucidate the exact pathophysiology.

Key Words: enuresis ‹› intravaginal ejaculatory time ‹› lifelong premature ejaculation

INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction. The prevalence rates of PE range from 20% to 40% among sexually active men in Europe and Asia [1–5]. PE causes interpersonal distress, diminished self–esteem, decreased sexual function and reduced quality of life [6, 7]. Lifelong PE is defined by the International Society for Sexual Medicine (ISSM) as "ejaculation that always or nearly always occurs before or within about one minute of vaginal penetration; inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" [8].

Enuresis is defined as involuntary nighttime bed wetting while sleeping in children 5 years of age and older. Enuresis is further divided into two subgroups, monosymptomatic and non–monosymptomatic. Monosymptomatic enuresis (ME) is nighttime bed wetting, without any accompanying daytime symptoms (e.g. constipation, polyuria, stress incontinence, abdominal straining, lower urinary tract symptoms such as frequency, urgency, urge incontinence, dysuria and weak urinary stream) [9]. The reported incidence of ME is 15% [10].

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Although certain psychological and biological factors are believed to be relevant in lifelong PE and ME, the exact etiology of both of these conditions has yet to be determined. Recent clinical research suggests an association and possible common pathophysiologic mechanisms between PE and ME; specifically that serotonergic pathways appear to be operational in both [11]. Several researchers have reported alterations in the activity of serotonin in the central and peripheral nervous systems, which may constitute a possible common underlying mechanism in PE and ME [12–15].

The study compares the intravaginal ejaculatory latency time (IELT) between lifelong PE men with and without ME and determines if there is an association between the severity of ME and duration of IELT.

MATERIAL AND METHODS

Study Population: Between November 2008 and March 2011, 164 patients were evaluated at our outpatient clinic with the complaint of PE. Of the patients, 10 did not report lifelong PE and 17 were not certain regarding their history of ME episodes. Consequently, 137 patients with lifelong PE enrolled in this study. All patients were diagnosed with lifelong PE according to the ISSM definition [8].

A focused general medical and urological examination was performed on all patients, and laboratory (urinalysis, biochemical tests including serum creatinine, lipid profile, fasting glucose level and hormonal profile including total and free testosterone) tests were performed in an effort to identify any underlying medical conditions associated with PE. Patients had their IELTs measured by their partner using a calibrated stopwatch for a month. The results of IELTs were tabulated. Of the patients enrolled, none reported erectile dysfunction (ED), reduced sexual desire, orgasmic dysfunction, psychiatric or chronic medical illness, alcohol or substance abuse, use of medication that may cause/treat PE, or history of urogenital surgery. All patients were married and in a stable, heterosexual relationship with the same partner for at least 6 months.

Concurrently, we asked patients if they had ME in their childhood and their estimated age of attaining nighttime urinary continence (AC). A detailed medical history was taken if they had a history of any disease, which could cause nocturnal enuresis in their childhood. We graded the frequency of enuresis using the following criteria: 1–2 times/week as infrequent; 3–5 times/week as moderate; and 6–7 times/week as severe. None of the patients with ME had a normal continence period prior to AC.

Written informed consent was obtained from all patients prior to commencement of the study, which was approved by the institutional review board.

Statistical methods

The characteristics and mean IELTs of PE patients with and without ME were compared using a student's t–test. Furthermore, the correlation between severity of ME and IELT in patients with ME was assessed with a trend test.

RESULTS

Patient characteristics are summarized in Table 1. Of the PE patients included, 57 (41.6%) reported ME (Group 1) and the remaining 80 patients did not report ME (Group 2). General characteristics of patients such as marital status, household income and education level did not differ between the two groups ($p = 0.972$). There was no statistical significance in age ($p = 0.096$), mean IELT ($p = 0.504$), or duration of PE ($p = 0.897$) in patients with and without ME. Of the patients with ME (Group 1), 16 (28.1%) had infrequent, 18 (31.6%) had moderate and 23 (40.3%) had severe enuresis. In Group 1, 36 patients reported a history of behavioral therapy for ME in their childhood, whereas the remaining 21 did not receive any other treatment. None of the patients in Group 1 continued to suffer from ME. There was a strong negative correlation between the severity of enuresis and IELT in patients with ME ($p < 0.0001$). IELT was shorter in patients with severe ME.

DISCUSSION

The objective of our study was to compare the IELTs in lifelong PE patients with and without ME and to determine if there was a relationship between the severity of ME and IELT. Our results demonstrate that IELT has a strong negative correlation between the severity of enuresis in lifelong PE patients with ME. Prior physiologic studies examining the mechanisms responsible for ejaculation and micturition, demonstrate similarities which may, in part, account for these findings.

Ejaculation is a complex neurological mechanism at both the spinal and cerebral levels [16]. Neurologically, the ejaculatory reflex requires sensory receptors, afferent pathways, cerebral, sensory, motor, and spinal motor centers, and efferent pathways [17, 18]. Ejaculation is mediated by the spinal control center under the inhibitory/excitatory control of supraspinal brain structures such as the hypothalamus and medial preoptic area [19].

Numerous studies have investigated the role of dopamine and 5–HT demonstrating neurochemical effects in modulating ejaculation [17, 20]. Serotonergic neurons are widely distributed in the central nervous system and are predominantly found in the brainstem, raphe nuclei, and reticular formation [17]. Serotonergic neurons modulate ejaculatory activity through 5–HT receptor subtypes, especially 5–HT_{1a} and 5–HT_{2c} [21]. Stimulation of the 5–HT_{2c} receptors results in a delay of ejaculation in male rats, whereas stimulation of post–synaptic 5–HT_{1a} receptors shortens ejaculatory latency. This foundation has lead to the hypothesis that men with PE may have hyposensitivity of 5–HT_{2c} and/or hypersensitivity of the 5–HT_{1a} receptors [12, 13, 22].

Serotonin exerts an important role in bladder control through central and peripheral mechanisms [23]. Activation of the serotonergic system inhibits the parasympathetic voiding pathway, which increases urine storage by central 5–HT_{1a} and peripheral 5–HT_{1c} receptors [24]. Some studies suggest that central 5–HT_{2c} receptor activation in rats inhibits micturition [25]. Serotonin inhibition also has an impact on micturition and ureteral peristalsis, by interfering with the spinal reflexes through 5–HT_3 receptor stimulation [14]. In an animal study, Testa et al. observed that stimulation of presynaptic 5–HT_{1a} receptors decreases the threshold for micturition, and blocking these receptors inhibits bladder activity [15]. The excitatory effect of the selective 5–HT_{1a} agonist, 8–hydroxy–2–tetralin (8–OH–DPAT), on ejaculation has been demonstrated in rats after systemic delivery [26]. This molecule revealed similar excitatory effects when injected directly into central brain areas (e.g. raphe nucleus) [27]. Guiliano et al. showed that 5–HT, in general, inhibits ejaculation, whereas stimulation of 5–HT_{1a} autoreceptors, blocks this inhibitory effect by decreasing the release of 5–HT in the synaptic cleft [21].

A delay in the maturation of sensory–motor neurons in the CNS, such as in the reticular formation, may cause a lack of awareness of bladder distension [28]. A study evaluating the relationship between ME and PE reported that the weak control of target organs by the cerebral cortex and the abnormal low threshold of sensory neurons in the intestine and genitalia may account for findings demonstrated in patients with PE, irritable bowel syndrome, or ME [29]. Ciftci et al. compared 60 patients with PE and 60 healthy men and demonstrated higher prevalence of ME in PE patients than the control group [30]. Recently, in a randomized prospective study, Gokce et al. revealed a higher prevalence of ME in patients with lifelong PE than observed in a healthy population and hypothesized that a common deficiency in inhibitory signal processing in the CNS may underlie both the inability to inhibit ejaculation and to control micturition [11].

Table 1. *The characteristics of lifelong PE patients with and without ME*

	With ME	Without ME
Number	57	80
Age (mean ±SD)	36.0 ±7.8	34.1 ±8.3
IELTs (mean ±SD seconds)	45.2 ±17.4	47.5 ±17.6
AC (mean ±SD)	7.9 ±1.3	3.4 ±0.5
Smoking	None	None
Education level		
Elementary (n)	2	4
High School (n)	4	10
University (n)	51	66
Marital Status	n	n
Married (n)	57	80
Household Income (TL)	2000–11200 TL	2200–11400 TL
Number of infrequent ME	16 (28%)	–
Number of moderate ME	18 (31%)	–
Number severe ME	23 (40%)	–

AC – age of urinary continenc; IELT – intravaginal ejaculatory latency time; ME – monosymptomatic enuresis; PE – premature ejaculation; TL – turkish lira

In support of the above findings, a common therapeutic efficacy is noted with the selective serotonin reuptake inhibitors (SSRIs) for both PE and ME, highlighting a potential shared mechanism of disease. Pharmacotherapy constitutes the basis of the treatment of lifelong PE and recent guidelines proposed chronic use of SSRIs because of their proven efficacy [31]. Chronic administration of SSRIs results in an increase of 5–HT levels in the synaptic cleft, which leads to desensitization of 5–HT_{1a} autoreceptors and a consequent inhibition on 5–HT release into the synapse [32]. The resultant effect of SSRI is more 5–HT release into the synapse, stronger enhancement of 5–HT neurotransmission, and consequently stronger activation of postsynaptic 5–HT receptors [33]. Treatment with fluvoxamine has demonstrated efficacy in children with ME, with suggested mechanisms involving enhanced control of emotional stress and depth of sleeping and subsequent relaxation of the detrusor muscle [34, 35].

The current study demonstrates several limitations including the absence of standardized questionnaires such as Premature Ejaculation Diagnostic Tool (PEDT) [36, 37] or Arabic Index of Premature Ejaculation for diagnosing PE [38]. Both of these questionnaires were developed prior to the ISSM definition of lifelong PE, and their specificities have been shown

to be rather low [39]. Hence, recent guidelines underline that these questionnaires should not take the place of a detailed sexual history, although they can be valuable adjuncts for clinical assessment [40] The study is also limited by recall bias with information obtained regarding prior ME episodes relying solely on patient recollection. As patients may have difficulty in remembering the details of their episodes of enuresis during childhood, and particularly the age at which they gained continence, leading to a concern about the reliability of the data. Surprisingly, the majority of the patients were quite specific about their ME history regarding the frequency and severity of episodes and AC. The patients who were not sure about their past ME episodes were excluded. The sample size of our study was relatively small and the data obtained is from one center. Therefore, further multicenter observational studies with more subjects will be required to provide additional evidence regarding the association between lifelong PE and ME.

CONCLUSIONS

A strong negative correlation exists between IELT and the severity of enuresis in patients with PE and ME. Further studies are required to confirm this interesting finding and elucidate the exact pathophysiology.

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