

Urologic symptoms and functional neurologic disorders

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Abstract

The term functional urologic disorders covers a wide range of conditions related broadly to altered function rather than structure of the lower urinary tract, mainly of impaired urine voiding or storage. Confusingly, for a neurologic readership, these disorders of function may often be due to a urologic, gynecologic, or neurologic cause. However, there is a subset of functional urologic disorders where the cause remains uncertain and, in this chapter, we describe the clinical features of these disorders in turn: psychogenic urinary retention; Fowler's syndrome; paruresis (shy-bladder syndrome); dysfunctional voiding; idiopathic overactive bladder, and interstitial cystitis/bladder pain syndrome. Some of these overlap in terms of symptoms, but have become historically separated. Psychogenic urinary retention in particular has now largely been abandoned as a concept, in part because of the finding of specific urethral electromyogram findings in patients with this symptom now described as having Fowler's syndrome, and their successful treatment with sacral neurostimulation.

In this chapter we review the poorly researched interface between these "idiopathic" functional urologic disorders and other functional disorders (e.g., irritable-bowel syndrome, fibromyalgia) as well as specifically functional neurologic disorders. We conclude that there may be a relationship and overlap between them and that this requires further research, especially in those idiopathic functional urologic disorders which involve disorders of the urethral sphincter (i.e., voluntary muscle).

INTRODUCTION

Functional neurologic disorders, such as functional tremor or functional limb weakness, are diagnosed based on positive signs, such as entrainment of functional tremor or Hoover's sign of functional leg weakness, which demonstrate an underlying intact structure to the nervous system. Confusingly, for a neurologic readership, there is much less of a dichotomy in the urologic literature between functional and structural disorders. The term functional urologic disorders covers a wide range of disorders in which abnormal functioning of the lower urinary tract (LUT) causes urologic symptoms.

Most functional urologic symptoms have a clear organic pathology (e.g., urologic, gynecologic, or neurologic) that is uncovered during clinical assessment or investigation. There are, however, some functional urologic disorders where the LUT dysfunction is evident through investigations, but the etiology is unclear.

Functional disorders of the LUT manifest as voiding dysfunction, storage dysfunction, or both. The symptoms of storage dysfunction include urinary urgency, daytime frequency, nighttime frequency, nocturia, and/or urge urinary incontinence (Abrams et al., 2002; Hayllen et al., 2010). Voiding dysfunction manifests with

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symptoms of urinary hesitancy, intermittent flow and slow stream, straining to void, a sensation of incomplete bladder emptying after voiding and double voiding, characterized by the need to urinate again soon after voiding (Abrams et al., 2002). In the most severe case, patients may even be in urinary retention.

We start this chapter with a description of LUT function in health and a summary of what is known about the brain–bladder axis. We then focus on the following presentations where there is no clear cause for dysfunction: psychogenic urinary retention; Fowler’s syndrome; paruresis (shy-bladder syndrome); dysfunctional voiding; interstitial cystitis/bladder pain syndrome, and overactive bladder (OAB). Some of these overlap in terms of symptoms, but have become historically separated.

We then discuss what evidence there is for an overlap between these disorders and functional somatic disorders such as fibromyalgia (FM) and irritable bowel as well as functional neurologic disorders such as functional movement disorders or dissociative (nonepileptic) seizures. Functional somatic disorders have been recognized in patients with idiopathic functional urologic disorders, and LUT dysfunction has also been documented in patients with a range of functional somatic disorders. The nature of the association, however, is uncertain and whether these are the manifestations of a common underlying abnormal working of the nervous system, or merely represent the coincidental existence of two independent processes, is yet to be systematically explored.

LOWER URINARY TRACT FUNCTIONS IN HEALTH

In health, the LUT remains in the storage phase, acting as a low-capacity reservoir of urine, 99% of the time. Storage is dependent on sympathetic and somatic-mediated contraction of the internal and external urethral sphincters, respectively, and sympathetic-mediated inhibition of the detrusor. During the storage phase, the pontine micturition center (PMC) is tonically inhibited by activity from cortical and subcortical centers, such as the prefrontal cortex, anterior cingulate gyrus, and insula (de Groat et al., 2015). Increasingly stronger signals through the sacral afferents during the storage phase are primarily responsible for initiating a switch to the voiding phase (Valentino et al., 2011). When deemed socially appropriate and safe, tonic inhibition of the PMC from the periaqueductal gray (PAG) is released, resulting in relaxation of the urethral sphincters and pelvic floor, and parasympathetic-mediated activation of the detrusor, voiding ensues (Panicker and Fowler, 2010).

CURRENT MODELS OF THE BRAIN–BLADDER AXIS

A more indepth review of the complex higher cortical pathways is useful to gain a better understanding of the bladder–brain axis and explore the association between functional disorders and LUT symptoms. Current understanding of LUT regulation suggests connection between the LUT and higher centers, including emotion, arousal, and motivation. Additionally, three circuits of micturition are postulated (Griffiths, 2015). The micturition system works largely unconsciously via PAG and parahippocampal regions of the temporal cortex to monitor the slowly filling bladder (Kavia et al., 2010; Tadic et al., 2013). Once it is socially appropriate and safe to void, activation of the medial prefrontal cortex triggers the PAG to activate the PMC. This circuit is hypothesized to be closely linked not only anatomically to the amygdala, but also emotionally linked to the crucial aspect of safety required for voiding.

In patients who experience the threat of involuntary leakage with or without the sense of urgency, two other circuits are activated. One involves the insula and prefrontal cortex. The insula is known to receive homeostatic information from the whole body, with increasing activation as the bladder progressively fills. The prefrontal cortex has connections to the limbic system, associated with emotional and social contextualized decision making and involved in working memory. In response to the threat of involuntary voiding, the medial prefrontal cortex is inhibited by activity from the insula and lateral prefrontal cortex. Reduced medial prefrontal cortex activation inhibits PAG activation and raises the threshold micturition level (Tadic et al., 2011).

The anterior cingulate gyrus is responsible for motivation and adjustments of bodily arousal states in response to mental stress. It is coactivated with the supplementary motor area, which controls striated muscles such as those in the pelvic floor and external urethral sphincter (Critchley, 2003). In response to the threat of involuntary voiding and the sensation of urge, activation of both the supplementary motor cortex and the dorsal anterior cingulate gyrus occurs. These two areas are thought to be responsible for simultaneous pelvic floor and urethral sphincter contraction and the anterior cingulate gyrus is thought to create the motivation to visit a toilet (Schrum et al., 2011).

The PAG is thought to play a significant role linking between higher centers and the LUT, with projections to the thalamus, hypothalamus, and amygdala, while also receiving information from the bladder (Griffiths and Fowler, 2013; Griffiths, 2015). The PAG modulates the voiding threshold using the information received from the higher centers. If it is unsafe or socially

inappropriate to void, the micturition threshold will be increased and the need to void reduced until there are higher bladder volumes. Brainstem nuclei such as the locus coeruleus modulate behaviors related to LUT function. The locus coeruleus system initiates and maintains arousal and facilitates shifts between focused attention and scanning attentiveness (Berridge and Waterhouse, 2003). Activation of the PMC and hence the locus coeruleus results in a switch from nonvoiding to voiding-related behaviour. Experiments in rodent models have shown that the expected pattern of increased activity from the locus coeruleus with increasing bladder pressure is lost 2 weeks after partial bladder outlet obstruction, even when bladder pressure increased to the micturition threshold (Rickenbacher et al., 2008). This may be relevant in understanding why some individuals with chronic urinary retention may have high volume retention without a sensation of urge or bladder fullness. It also suggests that persistent outlet obstruction leads to a loss of central regulation of LUT function.

As well as the loss of sensitivity to increases in bladder pressure, the locus coeruleus neurons also showed increased basal activity of 40% compared with sham rats (Rickenbacher et al., 2008). This elevated basal activity is associated with hyperarousal, difficulty focusing on an ongoing task, and neurobehavioral impairments such as anxiety and sleep impairment. Theta oscillations were prominent on electroencephalogram, which ties in with loss of ability to differentiate between differing bladder pressures. Theta oscillations play a role in sensorimotor integration by coordinating activity in various brain regions on the basis of sensory input to update motor plans (Caplan et al., 2003). The presence of these may also cause difficulty with nonbladder sensorimotor processing.

ASSESSMENT OF FUNCTIONAL UROLOGIC DISORDERS

History and examination are essential to consider potential urologic and gynecologic pathologies such as prostate enlargement, pelvic organ prolapse, tumors, or neurologic disorders such as multiple sclerosis, spinal pathology, or Parkinson's disease. A bladder diary aids with assessment of the functional bladder capacity, urinary frequency, and the number of leakage or urgency episodes. Noninvasive investigations such as uroflowmetry and measurement of the postvoid residual by ultrasound or in-out catheterization help to uncover voiding dysfunction and incomplete bladder emptying. Urodynamics helps to identify the pattern of LUT dysfunction, such as detrusor instability or voiding dysfunction, but does not necessarily inform the etiology. Although the majority of patients presenting with "functional"

problems with their bladder will have a cause identified during the course of investigations, many will not, and these are the disorders we consider in this chapter.

PSYCHOGENIC URINARY RETENTION

There are numerous causes for urinary retention; most commonly this arises in the setting of structural urologic lesions or an established neurologic disorder (Panicker et al., 2010; Smith et al., 2013). Reports of an association between psychologic factors and urinary retention began to appear in the 1800s, under the term "hysterical ischuria" (Charcot, 1877; Dejerine and Gauckler, 1913). We have found reports of 109 patients with a diagnosis of "psychogenic urinary retention," with the majority ($n=84$) reported prior to 1985. The diagnosis was made after medical investigations to exclude urologic, gynecologic, or neurologic causes (Margolis, 1965; Bridges et al., 1966; Blaivas et al., 1977; Barrett, 1978; Korzets et al., 1985; Nicolau et al., and 1991; Bilanakis, 2006). Triggering events and secondary gain were typically then sought and urologists were urged to look for recent life stressors and positive psychologic features to make the diagnosis (Wahl and Golden, 1963).

Psychogenic urinary retention was reported most commonly in young women, with an average age of onset of 29 years based on a review of 15 papers. Emotional deprivation during childhood seemed to be a predisposing factor in many cases (Wahl and Golden, 1963; Montague and Jones, 1979), and there were several reports of patients having nocturnal enuresis and urinary tract infections (UTIs) (Wahl and Golden, 1963; Lamontagne and Marks, 1973; Christmas et al., 1991).

The literature is replete with predisposing and precipitating factors, including perceived stress, such as unhappy marriage or home life (Montague and Jones, 1979; Korzets et al., 1985), feelings of guilt or fear of punishment, often for promiscuous sexual activity (Wahl and Golden, 1963; Montague and Jones, 1979), and depression and anxiety (Blaivas et al., 1977; Montague and Jones, 1979). Patients' unhelpful thoughts about genitourinary sensations as being "dirty" (Williams and Johnson, 1956) and "tense and unassertive" (Lamontagne and Marks, 1973) or "emotionally overcontrolled" (Montague and Jones, 1979) personalities were also felt to predispose to abnormal bladder functions. In several patients, urinary retention was precipitated by physical triggers such as UTI, road traffic accident, surgery, or childbirth (Cardenas et al., 1986).

Modeling from parents with genitourinary problems, sudden death of a friend or colleague from renal disease, iatrogenesis due to recurrent questions about urinary dysfunction, or minor symptoms which escalated with

frequent medical reviews were also reported (Norden and Friedman, 1961; Wahl and Golden, 1963). Rape (Williams and Johnson, 1956; Montague and Jones, 1979) and murderous rage (Williams and Johnson, 1956) were reported in only 2 patients, but are often quoted in case series introductions or discussions as potential precipitating factors.

Many patients reported unexplained sensory symptoms or pain and headaches (Williams and Johnson, 1956; Lamontagne and Marks, 1973; Montague and Jones, 1979). These symptoms improved with improving urinary symptoms. Psychogenic urinary retention was only associated with renal dysfunction in 2 cases (Knox, 1960; Korzets et al., 1985). Perceived benefits included freedom from unhappy home or sexual situations, the ability to exert control in situations in which the patient was being exploited, and being unburdened from many household duties expected of a woman at that time (Wahl and Golden, 1963; Montague and Jones, 1979).

Treatment outcomes were generally only published in patients who significantly improved. However, many patients underwent unnecessary surgery, such as urethral dilatation, urethral elongation, and hysterectomy before a diagnosis of psychogenic urinary retention was made and specific treatment commenced (Montague and Jones, 1979; Cardenas et al., 1986). It is unclear, however, what proportion of patients diagnosed with psychogenic urinary retention were left with a permanent indwelling catheter or escalating surgical options for long-term treatment (Blaivas et al., 1977). Treatment was initially described with psychoanalysis, but in more recent literature, studies of systematic desensitization with relaxation training and biofeedback-monitored relaxation training were described (Lamontagne and Marks, 1973; Montague and Jones, 1979; Nicolau et al., 1991).

Reviewing the literature, there are also case reports of psychogenic urinary retention, which in hindsight clearly had a nonpsychogenic cause. For example, a case was reported in 1891 of a young woman developing urinary retention and this was attributed to her being frightened by a man with a traveling bear. However, there was also mention of abnormal sensations of tight rings around her lower thighs, reduced sensation and power in her legs, and bowel disturbance, which gradually improved over 6 months (Little, 1891). It seems possible that this was due to an inflammatory conus lesion which would not have been diagnosed with the investigations at the time. The danger of making a diagnosis of psychogenic or functional neurologic disorder in the absence of positive signs, such as Hoover's sign of functional weakness, is highlighted by this case and caution should therefore be exercised when exploring this area. Although urinary

retention was included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 2000) as one of the symptoms of somatization disorder, there are few studies which refer to this condition in the recent literature.

FOWLERS SYNDROME

At a time when several of the cases of unexplained urinary retention were being labeled as "psychogenic," Clare Fowler and colleagues investigated the electromyogram (EMG) activity of the striated urethral sphincter and reported abnormal findings in 72% of the 48 women they examined (Fowler and Kirby, 1986). The findings they reported were complex repetitive discharges (CRDs) and decelerating bursts (DB), and this abnormal EMG activity suggested a biologic basis for urinary retention in young women who hitherto were told they had psychogenic urinary retention. Further investigation of this patient subgroup found that they were young women with an average age of 27 years, who, despite retaining urine, typically more than 1 liter, did not report urgency. They often reported an unpleasant sensation of "something gripping" during catheter withdrawal (and insertion), which was so severe that 28% of the original cohort received suprapubic catheters (Swin and Fowler, 2001). Two-thirds of patients reported a triggering event at the onset of retention, most commonly surgery but also childbirth, UTI, or an acute medical condition. Many women note a long history of voiding difficulty prior to their initial episode of urinary retention (Swin and Fowler, 2001). Subsequent investigations showed that women with an abnormal EMG often had a high urethral pressure profile and sphincter volume (Wiseman et al., 2002). The abnormality is thought to be a nonrelaxing striated urethral sphincter, which causes abnormally high urethral pressures and impaired voiding. Activation of sphincter afferents is likely to be having a reflex inhibitory effect on detrusor afferent and efferent activity, resulting in complete urinary retention and poor sensations of bladder fullness (Ramm et al., 2012). Our current understanding of the etiology of Fowler's syndrome is that it likely occurs due to upregulation of spinal enkephalins (Panicker et al., 2012), naturally occurring opiates, which reduce bladder sensation and negatively feed back to the sacral nerve roots, so that urethral sphincter sympathetic tone remains elevated and the PAG and PMC are not activated, even with large-volume bladder filling. The effect of upregulated spinal enkephalins is likely to be exacerbated by exogenous opiates.

The diagnosis is often difficult to establish and women with Fowler's syndrome see on average three consultants before their diagnosis is reached (Kavia

et al., 2006). Although the urethral sphincter EMG findings are characteristic for this condition, in recent years two papers and two abstracts, one of which was a 10-year follow-up of the first, reported that these findings may be seen in the external urethral sphincter of apparently healthy women (Kujawa et al., 2001; Ramm et al., 2012; Tawadros et al., 2015). The number of participants in these studies were small, but they do raise some interesting questions about the specificity of these EMG findings to Fowler's syndrome, and also the effects of the menstrual cycle on EMG changes. The finding of CRDs and DBs in apparently asymptomatic young women suggests that only when the inhibitory signal is sufficiently strong will urinary retention occur. The EMG changes should therefore be considered with the clinical features before making a diagnosis of Fowler's syndrome. The finding of an elevated urethral pressure profile (>92 – age cm water) or urethral sphincter volume (>1.8 cm³) aids the diagnosis (Wiseman et al., 2002). The finding of CRDs and DBs, however, remains prognostically useful as patients with these changes have improved outcomes following sacral neuromodulation (De Ridder et al., 2007).

The only currently useful long-term treatment for Fowler's syndrome is sacral neuromodulation, which has successful outcomes, with up to 70% of patients regaining the ability to void normally with postvoid residuals of ≤ 100 mL, on follow-up of up to 10 years (De Ridder et al., 2007; Elneil, 2010). Sacral neuromodulation appears to work by overriding the negative feedback from the sacral nerves. On imaging studies of 6 women with sacral neuromodulation, the previously reduced activity in the PAG and other higher brain centers shows restoration of normal or near normal activity after sacral neuromodulation insertion (Kavia et al., 2010). A recent open-label pilot study of 10 women demonstrated that urethral sphincter injection of botulinum toxin was associated with improvement in their urinary symptoms and objective improvements on urodynamic testing, and this potentially represents a less invasive option with few side-effects (Panicker et al., 2016).

Somatic comorbidities have been reported in women with Fowler's syndrome. A retrospective study of the hospital records of 62 women with Fowler's syndrome found that almost a quarter of patients (24%) with Fowler's syndrome had functional neurologic symptoms, including loss of consciousness, limb weakness, sensory disturbance, and memory impairment (Hoeritzauer et al., 2016). There are no comparison data in patients with other urologic or uro-neurologic disorders; however, based upon population prevalence of 2–33 per 100 000 for dissociative seizure (Reuber, 2008) or 1.7% of the population for patients with multiple idiopathic symptoms (Engel et al., 2002), this

represents a high degree of comorbidity burden. Further studies are required to explore the reasons for this, whether due to a long diagnostic limbo prior to diagnosis or possibly because patients with Fowler's syndrome are more likely to have functional somatic comorbidities. Patients with Fowler's syndrome may be missing a useful opportunity to treat their disorder in the context of other relevant comorbidities. In a separate prospective series of 62 patients treated with sacral neuromodulation, 26.6% of patients with Fowler's syndrome and 44% of patients with chronic idiopathic urinary retention screened with the Patient Health Questionnaire were defined as being at risk for somatization based upon their scores (De Ridder et al., 2007).

Fifty percent of patients with Fowler's syndrome suffered from unexplained chronic abdominopelvic, back, leg, or widespread pain (Hoeritzauer et al., 2016). A recent study of gynecologic pathology in patients with Fowler's syndrome found rates similar to that expected in the general population, so it is unlikely that these chronic pain syndromes were caused by an underlying undiagnosed pelvic pathology (Karmarkar et al., 2015).

PARURESIS

Paruresis, also called “shy” or “bashful” bladder syndrome, is defined by DSM-5 (DSM-5 300.23: American Psychiatric Association, 2000) as a social anxiety disorder (social phobia) characterized by fear and avoidance of urinating in public toilets when other individuals are present. It is characterized by a situation-specific voiding dysfunction which usually occurs in adolescence following an unpleasant experience such as being rushed to urinate or being teased or harassed (Hammelstein et al., 2005; Soifer et al., 2010). Awareness of others waiting for the toilet often further exacerbates symptoms. Paruresis is not associated with the fear of contamination (Vythilingum et al., 2002), and 20% of patients report no anxiety, but merely the inability to void in public toilets. Despite the subgroup with no anxiety, rates of psychologic comorbidity are quite high in the general paruresis population. Social anxiety disorders (29%), a major depressive episode (22%), alcohol abuse (14%), preparuresis obsessive compulsive disorder or significant problematic embarrassment all occur and should be sought (Vythilingum et al., 2002; Kaufman, 2005).

Paruresis is seldom investigated, and there is poor knowledge about the disorder in medical circles. However, it is associated with significant morbidity and patients report high levels of shame, limitations to activities such as traveling or dating, and professional work (Vythilingum et al., 2002). The prevalence and gender ratios are uncertain; however, men are more likely to seek

treatment and respond to questionnaires. Prevalence varies depending on how the question is phrased, as many as 6% of the population are fearful of using a public toilet (Ruscio and Brown, 2008), but situational inability to void seems to occur in only about 3% of the population (Hammelstein et al., 2005). Perhaps because of its low profile or the embarrassment associated with the condition, only about 30% of individuals seek treatment. Paruresis is often triggered by the triad of close physical or psychologic proximity with the individual, the presence of either familiar persons or the presence of strangers in the toilet, and temporary psychologic states, especially anxiety. Cognitive behavioral therapy with graded exposure techniques and biofeedback is the treatment offered for this condition (Rogers, 2003; Boschen, 2008; Soifer et al., 2010).

DYSFUNCTIONAL VOIDING AND HINMAN–ALLEN SYNDROME

Dysfunctional voiding is characterized by an intermittent or fluctuating urinary flow which occurs due to involuntary intermittent contractions of the striated urethral sphincter and/or levator muscles during voiding in otherwise neurologically intact individuals (Jeong et al., 2014; King and Goldman, 2014).

Despite this being primarily a problem of voiding, individuals with dysfunctional voiding, who are most often females, commonly present with symptoms of urgency and frequency. Incomplete bladder emptying is common, resulting in recurrent UTIs. Most patients have symptom onset from childhood.

The etiology is unclear; however, it is currently thought that dysfunctional voiding is a learned behavior in response to infection, trauma, detrusor overactivity causing stress incontinence, or psychologic factors (Karmakar and Sharma, 2014). Rates of depression and anxiety are greater than in asymptomatic controls (Fan et al., 2008) and dysfunctional voiding is more common in individuals with a history of sexual abuse (Ellsworth et al., 1995; Davila et al., 2003). Dysfunctional voiding is found in 2% of adults referred for urodynamic assessment, and the most common finding is a specific staccato pattern and dilated proximal urethra seen on voiding cystourethrogram (Glassberg and Combs, 2014). Treatment is primarily with biofeedback, which is thought to be successful in 60–90% of patients (Chin-Peuckert and Salle, 2001). However, a recent meta-analysis of all randomized studies of biofeedback ($n = 5$) for dysfunctional voiding in children has shown no benefit over controls (Fazeli et al., 2015). This may be due to poor trial data and the heterogeneity within the dysfunctional voiding group. Biofeedback is thought

to be much more successful in patients with involuntary intermittent contraction of the levator muscles.

A severe form of dysfunctional voiding, known as Hinman–Allen syndrome or nonneurogenic neurogenic bladder, is characterized by external urethral sphincter dysfunction, recurrent UTIs, and damage to the upper urinary tracts (Phillips and Uehling, 1993; Hinman, 1994). Hinman–Allen syndrome has been attributed to primarily psychologic causes since its inception. Children were described as having “failed personalities,” and parental divorce and “family disarray” were felt to be contributing factors (Hinman and Baumann, 2002). Up to 40% of patients have severe urinary tract morbidity, resulting in chronic renal failure (Yang and Mayo, 1997; Silay et al., 2011). The focus on psychologic etiology has been questioned with the publication of 9 cases of babies under 30 months having features of severe dysfunctional voiding (Jayanthi et al., 1997; Al Mosawi, 2007; Chaichanamongkol et al., 2008). There are moves towards allying this condition more closely to syndromes of elimination disorders such as urofacial syndrome (Ochoa syndrome or hydronephrosis with peculiar facial expression) (Ochoa, 2004; Roberts et al., 2014). Urofacial syndrome is a genetic disorder with similar findings on investigation to Hinman–Allen syndrome, but additionally patients have a characteristic facies on smiling, akin to crying (Ochoa, 2004; Roberts et al., 2014; Tu et al., 2014). It occurs due to an abnormality on chromosome 10 in the region of 10q23–q24 which codes for the genes *HSPE2* or *LRIG2* (Ochoa, 2004; Roberts et al., 2014). Only a small genetic study of 22 patients with Hinman–Allen syndrome has been performed and no abnormalities were detected; however, further studies are required (Bulum et al., 2015).

OVERACTIVE BLADDER

OAB is a syndrome defined by the International Continence Society as “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence in the absence of UTI or other obvious pathology” (Abrams et al., 2002). The diagnosis is made based upon the patient’s self-reported symptoms of urinary urgency, frequency, nocturia, and/or urgency urinary incontinence. Whilst urgency is difficult to measure clinically, urinary frequency is defined as voiding more than eight times per day, nocturia in OAB as passing small amounts of urine several times overnight, and urgency urinary incontinence can be recorded using a diary (Gormley et al., 2015). There are several conditions that may result in these symptoms; however, in a subset of individuals with “idiopathic” OAB, the cause remains obscure despite extensive investigations.

Patients with OAB report considerable morbidity. They have significantly worse health-related quality of life, are less likely than individuals without OAB to be employed, and may report sexual dysfunction (Ergenoglu et al., 2013; Tang et al., 2014). Patients with urinary incontinence (wet OAB) are more severely affected than those without incontinence (dry OAB). Disease-specific and global quality-of-life scores are lower and patients are less productive, and have greater health resource allocation (Tang et al., 2014). OAB is a long-term problem for the majority of patients and is underreported and undertreated (Getsios et al., 2005; Ergenoglu et al., 2013).

OAB is associated with high levels of anxiety and depression (Matsuzaki et al., 2012; Matsumoto et al., 2013; Vrijens et al., 2015). A recent systematic review reported a positive association between depression and OAB in 26/35 studies, and between anxiety and OAB in 6/9 studies. There was strong evidence of OAB developing in patients who had depression, with an odds ratio 1.15–5.78, although it was not possible to assess causality (Vrijens et al., 2015). The occurrence of OAB symptoms is associated with worse quality-of-life scores, embarrassment, and social isolation (Wagg et al., 2007; Tang et al., 2014).

Anxiety in healthy individuals can cause increased urinary frequency and urgency. Charcot and contemporaries used the term “pollakiuria” to describe “frequent and repeated micturition which one experiences under the stress of an emotion” (Dejerine and Gauckler, 1913). Animal studies suggested that chronic stress in anxiety-prone animals resulted in bladder hyperalgesia, which may contribute to the pathogenesis of LUT symptoms in affective disorders (Lee et al., 2015).

There is limited literature exploring LUT symptoms in patients with pathologic anxiety disorders. In one longitudinal community study, anxiety appeared to have a causative role in the occurrence of urge incontinence (Perry et al., 2006). Females aged over 40 years old were asked through a community postal survey about anxiety and depression using the Hospital Anxiety and Depression scale, and urinary symptoms, and followed up for a year. It was observed that the presence of urge incontinence and urinary frequency predicted the development of anxiety and depression. Moreover, anxiety predicted urge incontinence, whereas depression did not. In contrast, stress incontinence did not predict either anxiety or depression (Perry et al., 2006).

Four randomized controlled trials demonstrated that successful treatment of OAB resulted in a significant improvement in patients’ affective symptoms (Vrijens et al., 2015). The relationship between depression, anxiety, and OAB is postulated to be due to altered serotonin and norepinephrine levels causing OAB. This is on the

basis of animal models demonstrating that serotonin and norepinephrine have a modulatory effect on Onuf’s nucleus, which prevents accidental voiding when abdominal pressure increases, that serotonin inhibits the parasympathetic voiding activity and stimulates sympathetic activity, and that frequency is reduced after administration of selective serotonin reuptake inhibitors (Redaelli et al., 2015).

An alternative mechanism is through the central effect of increased corticotropin-releasing factor, released due to dysregulation of the hypothalamic–pituitary–adrenal axis, causing both bladder and mood symptoms, as seen in rodent models (Wood et al., 2013).

Recently three studies investigated functional somatic syndrome comorbidities in OAB and found irritable-bowel syndrome (IBS) occurring in up to one-third of patients with OAB, with a background population rate of 20% (Matsumoto et al., 2013). Patients with fibromyalgia (FM) were significantly more likely to have OAB and more severe OAB symptoms correlated to more severe FM symptoms. There was a significant overlap between OAB and functional dyspepsia in population-based studies (Persson et al., 2015). A history of sexual abuse was found to be associated with urinary frequency, urgency, and nocturia in at least three studies (Davila et al., 2003; Fitzgerald et al., 2007; Link et al., 2007). Among these studies, one fulfilled the Bradford Hill criteria for causality (Link et al., 2007).

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND FUNCTIONAL SOMATIC SYNDROMES

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by the Society for Urodynamics and Female Urology as “an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable cause” (Hanno et al., 2011). Voiding helps to reduce pain (Hanno et al., 2011). Patients with IC/BPS have a worse quality of life compared to healthy individuals, as well as to patients with OAB, due to effects on emotion, social limitations, and personal relationships (Kim and Oh, 2010).

Several studies have shown that patients with IC/BPS report comorbidities with functional somatic disorders such as IBS, FM, chronic fatigue syndrome (CFS), and vulvodynia (Aaron and Buchwald, 2001; Buffington, 2004; Rodríguez et al., 2009). Moreover, patients reporting an increasing number of functional somatic syndromes, particularly FM, CFS, and IBS, have a greater risk for IC/BPS (Warren et al., 2011). In a systematic review, 16 of 25 publications found overlap between

painful urologic pelvic pain syndromes and nonurologic syndromes (Rodríguez et al., 2009). Four studies were of patients with IC, and these showed higher rates of IBS (22.5% vs. 7% of controls), higher rates of backache, dizziness, arthralgia, abdominal cramps, and headache than controls, generalized pain in 27% vs. 7% of controls, and the women with IC were 11 times more likely to be diagnosed with IBS compared with controls. In patients who had FM, 12% of patients met the criteria for IC, and in patients with chronic pelvic pain, IBS was found in 22.4% of patients, 40% of whom had IC. Twin studies found that twins with fatigue were 2–20 times more likely to have IC than twins without fatigue (Rodríguez et al., 2009). Most of the studies exploring the association of LUT symptoms and functional somatic syndromes have focused on pain disorders and therefore the association of IC/BPS and functional somatic symptoms may be overrepresented in the literature.

There is also evidence for disproportionate levels of sexual abuse, high levels of depression, and panic disorder in patients with IC/BPS (Peters et al., 2007; Clemens et al., 2008). Several studies have investigated the association between abuse and IC/BPS. Physical, mental, or sexual abuse was found in 37% of patients with IC vs. 24% of symptom-free controls, and sexual abuse occurred in 18 vs. 8% in a population responding to a survey ($n=215$ vs. $n=464$ symptom-free controls) and 25/76 women (33%) seen in clinic (Peters et al., 2007).

There is no definitive treatment for IC/BPS. Treatment is tailored to the individual patient, with holistic multimodal multidisciplinary input to maximize efficacy. First-line treatments include stress reduction, patient education, use of nonprescription analgesics, pelvic floor relaxation, and dietary manipulation (De Bock et al., 2011).

Oral medications are generally the first-line treatment therapy, including antiallergics, amitriptyline, pentosan polysulfate sodium (Elmiron) and immunosuppressants. The choice of analgesic should be made in collaboration with a specialist pain management team. In case of failure of oral therapy, intravesical drugs (local anesthetics, hyaluronic acid, heparin) are administered; the intravesical route improves drug bioavailability, establishing high drug concentrations at the target, and is associated with fewer systemic side-effects. Disadvantages include the need for intermittent catheterization, which can be painful in BPS patients, cost, and risk of infection. Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scanty. It can be a part of the diagnostic evaluation, but has a limited therapeutic role. Botulinum toxin A may have an antinociceptive effect through bladder afferent pathways, producing symptomatic and urodynamic improvement (Engeler et al., 2015). Sacral neuromodulation is associated with

improvements in the symptoms of refractory BPS, with good long-term success seen in 72% (Engeler et al., 2015). Endourologic destruction of bladder tissue aims to eliminate urothelial lesions, mostly Hunner's ulcers, and can be helpful in the relief of pain and urgency. Ablative organ surgery should be a last resort and should be performed only by surgeons knowledgeable about BPS. Unfortunately, no single treatment seems to work for patients over a prolonged period of time (Hanno et al., 2011).

The etiology of IC/BPS is unclear and, whilst many studies have investigated association, causality remains elusive. Discussion of etiology involves physiologic and psychologic hypotheses (Aaron and Buchwald, 2001; Warren, 2014). The current favored hypothesis is that central brain processing of pain is different in patients with IC than in healthy controls. A recent imaging study using voxel-based morphometry of 33 patients with IC and no other comorbidities showed increased gray matter in the supplementary motor area, the superior parietal lobule/precuneus bilaterally, and the right primary somatosensory cortex. In the right primary somatosensory cortex volume changes also correlated with clinical measurement of pain, anxiety, and urologic symptoms (Kairys et al., 2015). It was suggested by the authors that increased gray matter in the precuneus might be caused by alterations in the higher pain connections in a similar manner to those seen in FM. Alternatively, the increases could be due to bottom-up changes to the higher-center connections caused by prolonged severe pain.

FREQUENCY OF UROLOGIC SYMPTOMS IN FUNCTIONAL/PSYCHOGENIC DISORDERS

Although rarely reported in the literature, LUT symptoms have been observed in patients with functional neurologic disorders. The only study of LUT dysfunction in patients with functional neurologic disorders is a retrospective review of 150 patients diagnosed with definite or probable functional movement disorders between 2006 and 2014 from the National Hospital for Neurology and Neurosurgery in London (Batla et al., 2016). Patient notes were screened retrospectively and patients with LUT symptoms were administered questionnaires for urinary symptoms and LUT-related quality of life. Thirty of the 150 patients with functional movement disorders had LUT symptoms; 20 of the 49 (41%) patients with fixed dystonia, 8 of the 57 (14%) patients with tremor, and 2 of the 14 (14%) patients with mixed movement disorders. LUT questionnaires were completed by 22 of the 30 patients, all of whom were female, the majority of whom had symptoms of OAB ($n=14$). The remaining

patients complained of stress urinary incontinence ($n = 5$) and low stream ($n = 3$). Opiate use was correlated with low stream ($p = 0.02$). The 5 most severely affected patients, 3 of whom had urinary retention and recurrent UTIs, and all of whom were using opiates, underwent urodynamic evaluation. No clear pattern of abnormality was evident and no neurologic or urologic cause was found. The 3 patients with urinary retention were initially managed with suprapubic catheterization and then had successful outcomes with sacral neuromodulation. Patients with fixed dystonia had the most severe symptoms, but the quality of life for all patients was negatively affected. LUT symptoms in other neurologic disorders are known to negatively affect quality of life; further studies in patients with functional neurologic disorders are required (Panicker and Fowler, 2015).

OPIATE USE AND LUT DYSFUNCTION

Pain is a well-known comorbidity in many functional conditions and high rates of prescription opiate use have been described (Pearson et al., 2014). The association between opiate use and LUT dysfunction is less well known amongst general physicians and patients, and could be contributing to LUT dysfunction in patients with neurologic and urologic disorders (Elneil, 2010; Panicker et al., 2012). In a study of 61 consecutive female patients reviewed at Queen's Square with unexplained urinary retention, 24 patients were taking regular opiates, 3 of whom were taking more than one opiate. Five of these patients were diagnosed with Fowler's syndrome, but 13 of the patients had no known cause for their voiding dysfunction. Patients had been prescribed opiates for unexplained predominantly abdominopelvic, musculoskeletal, or mechanical pain syndromes (Panicker et al., 2012). On discontinuing opiates, 2 of the 24 patients reported improvement in LUT symptoms. Intravenous ($n = 72$) (Malinovsky et al., 1998) and intrathecal ($n = 45$) (Kuipers et al., 2004) opiates have been shown to reduce bladder sensation, increase residual volume, and affect the urge to void and the ability to micturite in some patients, with dose-dependent effects (Kuipers et al., 2004). Opiates are thought to affect the bladder peripherally by increasing parasympathetic tone and centrally acting on spinal enkephalins and mu receptors in the PAG (Matsumoto et al., 2004).

IS THERE AN ASSOCIATION BETWEEN LUT DYSFUNCTION AND FUNCTIONAL DISORDERS?

The term "functional disorders" encompasses overlapping syndromes including CFS, FM, IBS, myofascial pain, and temporomandibular joint disease (Clauw, 2010). The overlap of symptoms is well documented

(Wessely et al., 1999; Clauw and Crofford, 2003; Wessely and White, 2013). The way in which these conditions overlap with functional disorders seen in neurologic practice, such as functional movement disorder and dissociative (nonepileptic) attacks, is also now well documented.

Reflecting on the LUT dysfunction discussed in this chapter and its relationship with functional disorders, the initial problem is the dearth of studies that have attempted to specifically answer the question as to whether functional urologic disorders could share an etiology with functional neurologic and somatic disorders.

It is known that the LUT is regulated by a complex interconnected network of higher centers involved in arousal, focus, understanding of safety and social propriety, emotion and motor activity. This system is informed by afferent signals from the LUT via the spinal cord, and the PAG and PMC are important brainstem centers involved in the coordination of urethral, pelvic floor, and detrusor contractions. There are many points at which this network can go wrong, yet present with a limited repertoire of LUT symptoms. Understanding of the bladder-brain axis is exponentially increasing through basic, clinical, and imaging science. Increasing knowledge of neural networks has changed the understanding of disease from simply biologic or psychologic processes to an awareness of disease as something spanning both, and affected by environment and beliefs, as well as genes, which all come together to create the patient's disease phenotype. In functional neurologic disorders, the field is moving away from the dualistic understanding of psychogenic versus organic etiology. This allows a functional model to emerge that comfortably incorporates psychologic and physiologic disturbances.

Considering whether these disorders have features which overlap with functional somatic syndromes, such as IBS, FM, or hyperventilation syndrome, the criteria from Wessely et al. (1999) will be used.

Patients with one functional syndrome frequently meet diagnostic criteria for other syndromes

The prevalence of other functional disorders in patients with OAB, IC, paruresis, and Fowler's syndrome has been discussed above.

Sex

IC, idiopathic OAB syndrome, Fowler's syndrome, and dysfunctional voiding affect predominantly women, whereas paruresis is likely to affect men more often. Some functional neurologic disorders such as functional propriospinal myoclonus have a male preponderance (van der Salm et al., 2014).

Emotional problems

Depression and anxiety are reported more in patients with idiopathic OAB, IC, paruresis, dysfunctional voiding, and Fowler's syndrome compared to healthy controls. However, the impact of a chronic LUT disorder on mood requires further study before attempting to make an association between psychological comorbidities and urologic disorders.

Physiology

Much of the current research of IC, idiopathic OAB, and Fowler's syndrome hypothesizes that there is a central mechanism (brain \pm spinal cord) causing the disorder rather than an abnormality which is solely bladder-based (Kavia et al., 2010; Tadic et al., 2011; Kairys et al., 2015). Paruresis is treated with cognitive-behavioral therapy, recognizing that a central mechanism of inhibition exists that must be unlearned.

History of childhood abuse or neglect

While this is frequently referenced in older psychogenic urinary retention literature, there are few studies which explore this, except in the IC and dysfunctional voiding literature (Ellsworth et al., 1995; Davila et al., 2003; Mayson and Teichman, 2009). In the Boston Area Community Health study ($n=5506$), sexual and physical abuse and the prevalence of urinary frequency, urgency, and nocturia met the Bradford Hill criteria to suggest causality (Link et al., 2007). Given the frequency of these urinary symptoms in the population, background rates of childhood and adult adversity and potential pathophysiologic mechanisms should be investigated in a range of neurologic, gynecologic, and functional urologic conditions.

Many patients with idiopathic functional urologic disorders share similar characteristics with patients who have functional somatic disorders. The LUT is unique amongst visceral organs because of the highly organized central neural network that regulates its functions and affords higher-level voluntary input, and therefore it is likely that there exists an association between LUT dysfunction and functional syndromes. Though tests such as urodynamics help to uncover the pathophysiologic correlate of LUT symptoms, the test is unable to provide information about the etiology or behavioral underpinnings responsible for the LUT dysfunction. Studies are therefore required that are designed to specifically evaluate the nature of the association between LUT dysfunction and functional syndromes and explore causality. Recognizing the interface between emotion, motivation, memory, and LUT functions would allow for a more

comprehensive approach to patients presenting with functional disorders.

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