

Fowler's Syndrome and Chronic Urinary Retention in Women

Running title

Fowler's Syndrome- a review

No relevant disclosures by any of the authors

Abstract

Key Content

- Urinary retention is a relatively uncommon presentation in young women.
- Fowler's Syndrome is an uncommon cause for urinary retention and women are often found to have an abnormally elevated urethral pressure profile, increased urethral sphincter volume and characteristically abnormal EMG of the urethral sphincter.
- The most effective treatment that has been found to restore voiding in women with Fowler's syndrome is sacral neuromodulation.
- Sphincter injections of botulinum toxin is a possible outpatient-based alternative.

Learning objectives

- To discuss the causes for urinary retention in young women
- To review the typical symptoms and signs associated with Fowler's Syndrome
- To share the current understanding about why this condition may occur
- To understand how to evaluate and treat a woman with suspected Fowler's Syndrome

Ethical issues

In a woman presenting with unexplained urinary retention, Fowler's Syndrome should be considered in the differential diagnosis, as the condition is potentially amenable to treatment

Key Words

Fowler's Syndrome, EMG, sacral neuromodulation, botulinum toxin

Word count 2451

Introduction

Urinary retention is relatively uncommon in young women, however if urological and neurological disorders have been excluded, the possibility of Fowler's Syndrome (FS) should be considered. The syndrome was first described by Fowler et al. in 1987 and originally comprised of complete urinary retention with the finding of a particular pattern of electromyographic (EMG) activity recorded with a concentric needle electrode from the striated urethral sphincter, in a young woman with clinical features of polycystic ovaries (1). Prior to this report, there had been several reports of "psychogenic urinary retention in women" and it was often considered in medical circles that urinary retention in young women was due to "hysteria" (2), (3), (4). Nowadays, if neither the urologist or neurologist can discover an underlying abnormality, the woman may be told she has Fowler's syndrome without any positive identification of that condition. However in a series of women presenting with retention and investigated in the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery, only about one third were confirmed to have FS (Figure 1) (5). The diagnosis is made based on a characteristic clinical history and confirmed by laboratory investigations.

Clinical features of Fowler's Syndrome

Swinn et al. carried out a retrospective study that has served to define the characteristic features of FS (6) (Table 1). Typically, young females post-menarche are unable to void and present with painless urinary retention. On evaluation, they often demonstrate post-void residual volumes in excess of 1 litre at some stage and although they may experience pain, they do not report the expected urgency at such

a large bladder capacity. Straining does not help empty the bladder and intuitively women feel they must promote sphincter relaxation to void by whatever means they can.

Women with FS who catheterise often find this painful, particularly on withdrawal of the catheter, with many women complaining of a sensation of “something gripping”. The difficulties may be so extreme that a suprapubic catheter may be required.

Women may also present with a picture of impaired voiding, complaining of predominantly voiding difficulties with or without incomplete bladder emptying, and together with symptoms of obstructed voiding may have increased urinary frequency and occasionally urgency but rarely becoming incontinent.

Women with FS often report an antecedent event prior to the onset of urinary retention. Most often an obstetric, gynaecological or urological surgical procedure using regional or general anaesthesia, but may be distant from the pelvis such as a tooth extraction. This suggests that the significant factor is the anaesthetic. Why this should occur is uncertain, however this is undoubtedly a source of medico-legal complaints. Some women may report a history of poor voiding with an interrupted flow before the onset of retention, and a common observation with women noticing it takes them longer to pass urine than others. Although not a troublesome feature, it is an important part of the history as it would suggest a pre-existing abnormality.

Many of the women reported in the original description of Fowler’s Syndrome were observed to be hirsute, obese and to have menstrual irregularities and there appeared to be a clinical association with polycystic ovaries (PCO) (1). This suggested the possibility of a hormonal basis for the abnormal sphincter relaxation in

FS. Variability in the degree of abnormal EMG activity has in fact been reported between the proliferative and luteal phases of the menstrual cycle in apparently asymptomatic women, supporting the notion that urethral sphincter activity may be influenced by hormonal activity (7). Developmentally, the distal urethra has been shown to be a constituent part of the clitoris, forming the “clituro-urethrovaginal complex” and clearly the distal urethra has major sex determined attributes (8, 9).

In a recent retrospective chart review, high levels of co-morbidities have been reported in women with FS. Nearly 50% of patients reporting some pain and other co-morbidities included psychological symptoms and probable functional disorders (10) but the report does not include any data following successful neuro-stimulation surgery, when anecdotally many of these other co-morbidities seem to resolve. Gynaecological pathology is reported and subfertility was more prevalent in women with FS compared to controls (11).

The reader is referred to the website <http://www.fowlersyndrome.co.uk/> which provides more information about FS.

Investigations

Urodynamics

Routine cystometry usually demonstrates a large capacity bladder without the usual sensations during the filling phase, and filling is often stopped by the urodynamicist at 500 ml on grounds of safety, although the subject’s actual functional capacity is much greater. The patient is unable to pass urine and so the conclusion might be

reached from the pressure flow study that the woman has an “acontractile” detrusor. However this is not always “true” acontractility, but rather detrusor underactivity, which is defined by the International Continence Society as “a contraction of reduced strength and/or duration resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time-span” (12). Detrusor underactivity is a common urodynamic finding in women with FS and additional findings of a high UPP help to differentiate this group. There is some evidence to suggest that patients with detrusor acontractility are more likely to fail SNM than those with detrusor hypocontractility (13). Drossaerts et al. go on to suggest that conventional urodynamics over-estimates the patients diagnosed with a hypocontractile or acontractile bladder (13) and therefore a more prolonged urodynamics recording, ie. ambulatory urodynamics, may play a role to better characterise the degree of detrusor underactivity in this group and predict outcome.

Urethral pressure profilometry

The maximum urethral closure pressure (MUCP) is typically found to having resting values in excess of 100 cm of water in women with Fowler’s syndrome(14). Based on the work of Edwards and Malvern in 1974, the formula of $92 - \text{age (in years)}$ is used to derive the expected pressure (15). In modern day practice, it seems curious that this almost arbitrary and operator dependent value of expected versus measured MUCP is used by Urologists in order to guide the implantation of a sacral neuromodulator device. Further clinical studies are needed to establish the role of urethral pressure profilometry in the evaluation of Fowler’s syndrome and whether an elevated MUCP may predict outcomes following sacral neuromodulation.

Urethral sphincter ultrasound

Although initial findings suggested that transvaginal ultrasound measurement of sphincter volume was helpful to detect the hypertrophy of the striated sphincter resulting from sustained overactivity(14), a subsequent view is that the test is highly subjective. With the development of new techniques such as 3D ultrasonography, it may again prove to be a valuable test. Performing the test however allows the opportunity for the sphincter and urethra to be carefully examined and sometimes identify other possible causes of urinary retention such as a urethral diverticulum. Other imaging modalities may have a role in the accurate assessment of sphincter volume, such as MRI; albeit a far more expensive technique than ultrasound.

Urethral Sphincter EMG

Concentric needle electromyography (EMG) of the striated urethral sphincter is diagnostic for FS and detects a particular type of abnormal activity. Although this sounds superficially like myotonia, detailed analysis show that the characteristic descending sound is due to a decelerating component of a complex repetitive discharge (CRD)(16). When a number of generators of this type of activity are heard, the sounds of these decelerating bursts (DB) are likened to that of underwater recordings of whale songs. Complex repetitive discharges without deceleration produce a sound like helicopters over the audio-amplifier of the EMG machine. Single fibre EMG analysis of CRDs showed that the jitter between the potentials is so low that it is likely there is on-going, ephaptic transmission between muscle fibres

generating repetitive, circuitous, self-excitation(16). It is this abnormal activity which is thought to cause involuntary contraction of the striated sphincter and activation of sphincter afferents. The involuntary contraction prevents relaxation of the sphincter, and causes abnormally high urethral pressure and impaired voiding, while the activation of sphincter afferents has a reflex inhibitory effect on detrusor efferents (possibly mediated by spinal endorphins) and result in complete urinary retention. Thus retention is a secondary effect of the abnormal sphincter contraction and only when the strength of the inhibitory signal is sufficient, will retention occur. The finding therefore of CRDs and DB activity in apparently asymptomatic young women, does not invalidate the significance of the finding of the EMG activity in the context of urinary retention in a young woman. (7).

The differential diagnosis for a woman presenting in chronic urinary retention

Structural causes for urinary retention are rare in women. Bladder outlet obstruction maybe due to external lesions which compress the urethral lumen, including urethral diverticula, uterine and cervical fibroids and vaginal wall cysts. Internally, urethral obstruction can be caused by urethral stricture disease or rarely urethral tumours such as carcinoma.

Functional disorders affecting the LUT are most commonly associated with neurological disease and in general, urinary symptoms are accompanied by other neurological symptoms and signs. Spinal cord lesions often manifest with incomplete bladder emptying, although the clinical picture is dominated by poor mobility and urge incontinence. The presence of spinal dysfunction can be

corroborated by clinical examination or tests such as MRI of the spine and lower limb evoked potentials. Retention may occur, however, in the stage of acute spinal cord injury, which is due to detrusor areflexia and lasts a few weeks. However, voiding dysfunction is a prominent feature in patients with lesions of the conus medullaris or following damage to the cauda equina. Incomplete emptying or complete retention can also result from small fibre involvement of diabetic or amyloid neuropathy. Retention may occur following surgical damage to the ganglia and post ganglionic fibres during radical pelvic surgery.

Incomplete bladder emptying is a feature of one of the Parkinson-plus syndromes, Multiple System Atrophy (MSA). An increasing post void residual volume is demonstrated as the disease progresses, accompanied by parkinsonian or cerebellar ataxia, and patients may go into complete retention (17).

Women with FS often report lower bowel dysfunction and another differential diagnosis is Chronic idiopathic pseudo-obstruction (CIPO), a rare syndrome characterized by gross distension predominately of the small bowel without any anatomical or mechanical obstruction where LUT dysfunction has been reported in up to 10-69% of patients (18), (19), (20) and urodynamic investigations may reveal detrusor hypocontractility (18).

Recently, an association between opiates and the onset of urinary retention has been noticed. In a series of 62 women coming to our clinic with retention, about one third (Figure 1), were taking some form of prescription opiate for pain relief, including tramadol, pethidine, morphine (proprietary names including Morphgesic SR, MXL, Zomorph, MST, Sevredol, Oramorph) or Fentanyl patches(5). The medication was usually started at a pain clinic where the woman had been referred with chronic back

pain or pelvic pain, often attributed to endometriosis. Importantly, only one third of women had FS, however a quarter of the women with the condition were taking opiate medications. It seems highly likely that exogenous opiates supplements the abnormally high levels of spinal endorphins which mediate the inhibitory effect of sphincter afferents activation (21).

Table 2 lists the causes for chronic urinary retention in women.

Treatment

Catheterisation

Catheterisation remains the mainstay of management for chronic urinary retention. Intermittent catheterization (IC) is the preferred mode and the frequency of using catheters depends upon the degree of incomplete bladder emptying. Women with FS may report difficulties in performing catheterisation, especially whilst attempting to remove the catheter, and therefore an experienced health care professional should be involved in teaching IC and an indwelling catheter such as a suprapubic catheter may be required if IC is found not to be suitable (22).

α -Adrenoreceptor blockers

A single study has demonstrated that using tamsulosin in a cohort of women presenting with voiding dysfunction was associated with improvements in voiding symptoms, flow rates and post-void residuals (23), though in clinical practice these medications have not been found to be beneficial in women with FS.

Sacral neuromodulation

The only treatment that has been found to restore voiding in women with FS is sacral neuromodulation (SNM). This technique involves the delivery of electrical current to activate or inhibit the neural reflexes associated with lower urinary tract function via stimulation of the S3 nerve root, which innervates the lower urinary tract (LUT) and pelvic floor.

Of a cohort of 60 women undergoing percutaneous nerve evaluation (PNE) and subsequent implant, 70% were voiding spontaneously when followed up with a mean interval of 7 years (24). This is in keeping with the findings from other centres of the longer-term efficacy of SNM as a treatment for non-obstructive retention, van Voskuilen et al. showing 76.2% efficacy at 70.5 months (25) and Elhilali et al. showing efficacy of 78% at 77 months (26). More recent studies following up patients for a mean period of 46.8 months suggest that success rates with SNM in patients with idiopathic retention due to FS was 73% and for those without a diagnosis of FS being 58%, respectively (27). De Ridder and colleagues observed that women with urinary retention who also had an abnormal sphincter EMG had a better outcome with SNM at 5 years (28).

SNM is now a minimally invasive procedure with the use of a permanent tined lead, which can be placed in the S3 nerve foramen under local anaesthesia and an implantable pulse generator (IPG) inserted in the subcutaneous tissue of the buttock region.

Over the last 20 years opinion has changed from thinking the stimulation “re-educates the pelvic floor” to more complicated theories about how the stimulation overcomes sphincter afferent mediated inhibition and so re-informs sensory parts of the brain and allows the LUT to be “switched on” again. Using functional brain imaging it was possible to show that the periaqueductal grey (PAG), a centre in the midbrain which receives sensory signals from the LUT, becomes activated in women with Fowler’s syndrome when the stimulator is switched on. Its re-activation seems to be linked to the patient’s report of a return of normal sensations from their LUT with the stimulator on (29) and restoration of detrusor contractions. This is supported by clinical evidence that women having success with SNM report restoration of bladder sensations within hours of switching on the device, followed by improvements in voiding (30).

Botulinum toxin

Though highly effective, SNM is an expensive, resource-intense surgical intervention, and complications are reported, with relatively high re-intervention rates (31). Initial reports of urethral sphincter injections of botulinum toxin nearly 20 years ago evaluated cautious dosages of botulinum toxin but concluded that the intervention was not effective (32). Over the years higher doses have been used,

with success in women without an established neurological or urological cause for urinary retention including women with a non-relaxing urethral sphincter (33) (34) (35). A recently conducted pilot study demonstrated an improvement in patient-reported lower urinary tract symptoms and objective parameters such as flow rate, post-void residual volume and MUCP ten weeks following urethral sphincter injections of onabotulinumtoxinA; no serious side effects were reported. It was proposed that blocking efferent signals from the sphincter by onabotulinumtoxinA may reverse the inhibitory effects (36). The results of this study suggest that this treatment could represent a possible outpatient based alternative in women for whom clean intermittent catheterisation is intolerable and sacral neuromodulation may not be possible.

An algorithm for the management of a young woman in urinary retention is presented in figure 2.

Conclusion

Fowler's Syndrome should be considered in the differential diagnosis for a young woman presenting with unexplained urinary retention. A definitive diagnosis is made based upon the results of specific investigations that evaluate the lower urinary tract and striated urethral sphincter. Treatment options such as sacral neuromodulation, and more recently sphincter injections of botulinum toxin, have been shown to be effective in managing urinary retention due to this condition.

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Table 1. Clinical features in young women presenting with urinary retention suggesting Fowler’s Syndrome

Key features
Age between onset of menarche and menopause, however usually presenting in the third decade
No evidence of urological, gynaecological or neurological disease
Urinary retention with volumes often >1000 ml
No sense of urinary urge despite high bladder volumes
Abdominal straining does not help with bladder emptying
Sensation of “something gripping” or difficulty on removing the catheter used for urinary drainage
No history of urological abnormalities in childhood or associated abnormalities of the urinary tract
Association with polycystic ovarian syndrome and endometriosis

Table 2. Causes for Chronic urinary retention in women

Structural	
<i>Tumours -</i>	
Leiomyomas	
Cysts of the vaginal wall or urethra	
<i>Other pathology</i>	
Urethral stricture	
Urethral diverticulum	
Urogenital prolapse	
Iatrogenic causes eg. following incontinence procedures such as suburethral tapes and Botulinum toxin injections	
Functional	
<i>Neurological causes</i>	
Multiple system atrophy	
Suprasacral spinal cord lesion resulting in detrusor sphincter dyssynergia	
Lesion of the conus medullaris or cauda equina	
Meningitis retention syndrome	

Radical pelvic surgery	
Small fibre neuropathy- diabetes, amyloidosis	
<i>Non-neurological causes</i>	
Fowler's Syndrome (FS)	
Chronic idiopathic pseudo- obstruction (CIPO)	
Medications- Opiates, drugs with anticholinergic properties	
Cause uncertain- postpartum urinary retention	

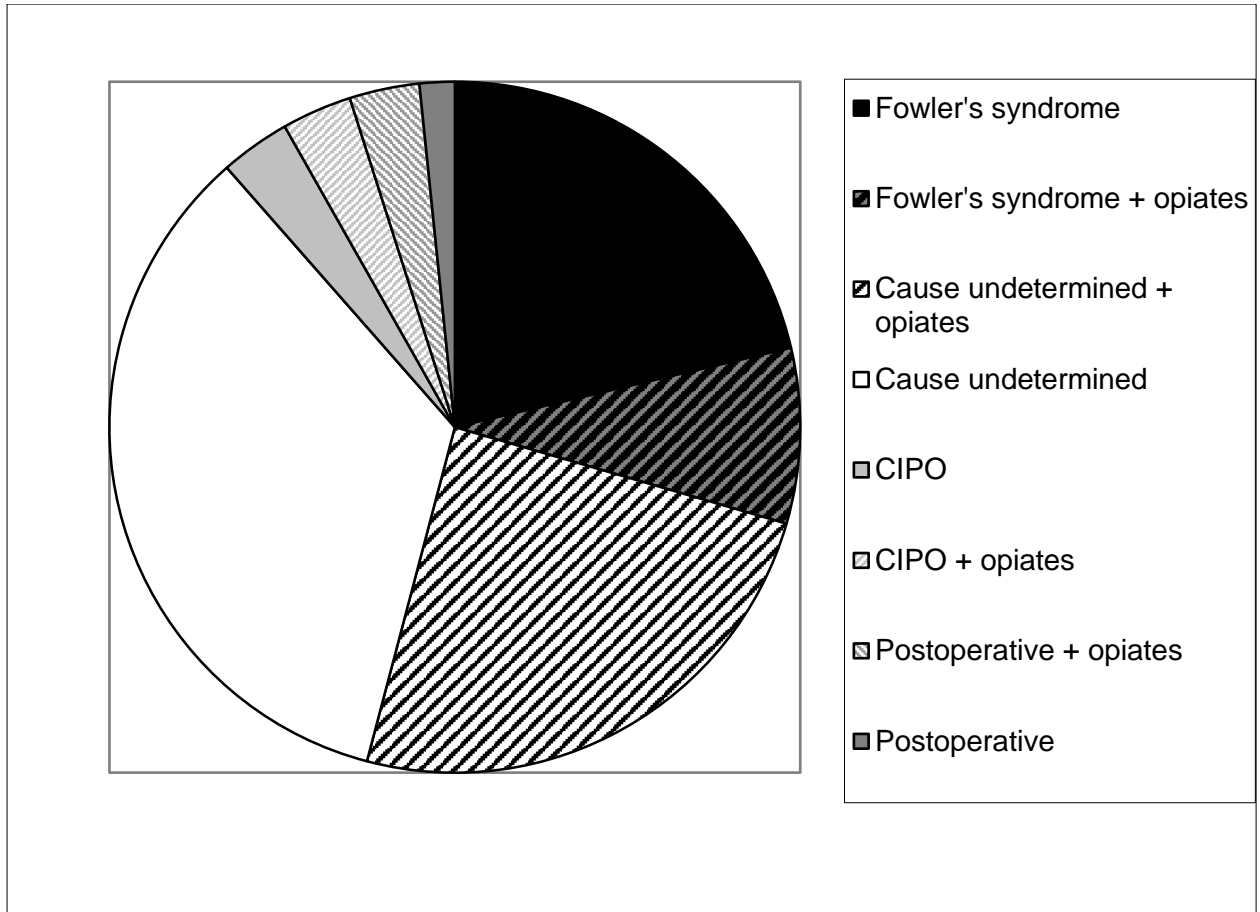


Figure 1

Causes for urinary retention in a series of women presenting in the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery, UCLH
(5)(requires permission)

Figure 2. Algorithm for the management of a young woman in urinary retention

(separate file powerpoint slide)

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