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UROLOGY – REVIEW

Urinary tract dysfunction in Parkinson's disease: a review

Lehana Yeo · Rajindra Singh · Mohan Gundeti · Jayanta M. Barua · Junaid Masood

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Abstract
Introduction Parkinson's disease is an extrapyramidal neurological disorder. Although motor symptoms are a predominant feature of the condition, non-motor symptoms have also been recognized. Urinary symptoms are frequently present in patients affected with Parkinson's disease (PD). Symptoms such as urgency, frequency, nocturia and urge incontinence significantly impact the patient's quality of life. We discuss the urinary dysfunction seen in patients with Parkinson's disease and consider the pathophysiology, important differentials, the investigations and management options for such patients.
Materials and methods An extensive search was performed using the PubMed®/EMBASE® databases to identify the available literature on urinary disturbances and Parkinson's disease. Reference was also made to current national guidelines on Parkinson's disease.
Results Urinary disturbances are frequently observed in sufferers of Parkinson's disease resulting in significant impact to the individual's quality of life. Studies report that storage symptoms are present in 57–83% of patients, whereas voiding symptoms are seen in 17–27% patients. Out of all the urinary symptoms, nocturia is the most common complaint in >60% patients with PD. Urgency occurs in 33–54% of patients, whilst frequency is experienced by 16–36% of patients. Detrusor overactivity (DO) is the commonest cystometric abnormality in patients with PD. The rate of neurogenic DO in patients with PD is 45–93%.The main differential to consider is Multiple System Atrophy (MSA) in which all patients are ultimately afflicted with urinary disturbance. It is well recognized that patients initially diagnosed with PD may in fact have MSA, and it is important to distinguish the two as their urological management is different. Patients presenting with refractory LUTS with concurrent PD should undergo full urodynamic investigation including cystometry, flowmetry and ultrasonography before treatment is initiated.
Discussion Referral to a urologist is advised in those with persistent or refractory urinary complaints. Urodynamic evaluation allows determination of the underlying bladder disorder; however, post-void residuals suffice in the uncomplicated patient. The pathophysiology of urinary dysfunction and current investigation and treatment modalities are discussed.

Keywords Urinary dysfunction · Parkinson disease · Review

L. Yeo · R. Singh · J. Masood
Department of Urology, Barts and The London NHS Trust, London, UK

M. Gundeti · J. M. Barua
King George Hospital, Ilford, Essex, UK

J. Masood (✉)
3 Taleworth Close, Ashtead, Surrey KT21 2PU, UK
e-mail: Junaido@aol.com

Introduction

Traditionally, motor symptoms have been the predominant feature of Parkinson's disease (PD); however, awareness of non-motor features, including bladder dysfunction, has increased. Urinary disturbances (UD) can be complex and difficult to manage, particularly as they may occur due to the disease process, medications used to treat the condition, or conditions unrelated to the disease, such as benign prostatic enlargement. Therefore, an understanding of bladder involvement in PD is crucial since UD can significantly impact the patient's quality of life [1].

It is not uncommon for individuals with PD to present to urologists and indeed the UK National Guidelines for Parkinson's disease recommend referral to urologists where bladder problems are refractory or persistent [2]. Whilst there have been reviews on the same topic published in the journals of Parkinsonism and Related Disorders, and Movement Disorders [3–5], they have targeted a neurology readership, and this review is aimed at urologists and provides further discussions on treatment options available.

PD is the most common cause of parkinsonism which is the neurological syndrome bearing the hallmarks of tremor, hypokinesia and postural instability. Other causes of parkinsonism include medications, toxins, metabolic diseases and atypical Parkinsonian syndromes like Multiple System Atrophy (MSA).

Urinary symptoms are more prominent in MSA and have an earlier onset; therefore, these patients are more likely to present to urologists. The pathophysiology behind MSA is different to that of PD and consequently management is different.

Parkinson's disease

PD is estimated to affect 100–180 per 100,000 of the population with an annual incidence of 4–20 per 100,000 [2]. Although motor symptoms are a predominant feature of the condition, non-motor symptoms are also recognized. A recent large multicentre study reported on the non-motor symptoms seen in patients with PD and found the occurrence rates were as follows: psychiatric symptoms 66.8%, sleep disturbances 64.1%, gastrointestinal disturbances and pain 61%, fatigue 58.1%, urinary dysfunction 57.3% and attention/memory deficits 44.7% [6].

Pathology

PD is associated with the degeneration of dopamine-producing cells in the substantia nigra of the midbrain and Lewy body formation. Braak et al. [7] proposed that the formation of intraneuronal Lewy bodies and Lewy neurites begins at two sites and continues in six stages, during which components of other systems become progressively involved. In stages 1–2, the Lewy body pathology is confined to the medulla oblongata/pontine tegmentum and anterior olfactory structures. In stages 3–4, the substantia nigra, other nuclei of the basal mid- and forebrain and the mesocortex are affected; the illness probably becomes clinically manifest during this phase. Finally, lesions appear in the neocortex in stages 5–6 [7].

Diagnosis

The definition of PD is a postmortem finding, and therefore, the diagnosis remains a challenge to neurologists. There is no premorbid diagnostic test, and the diagnosis is clinical. However, criteria set out by the UK Parkinson's Disease Society Brain Bank are widely accepted for the diagnosis of PD [2].

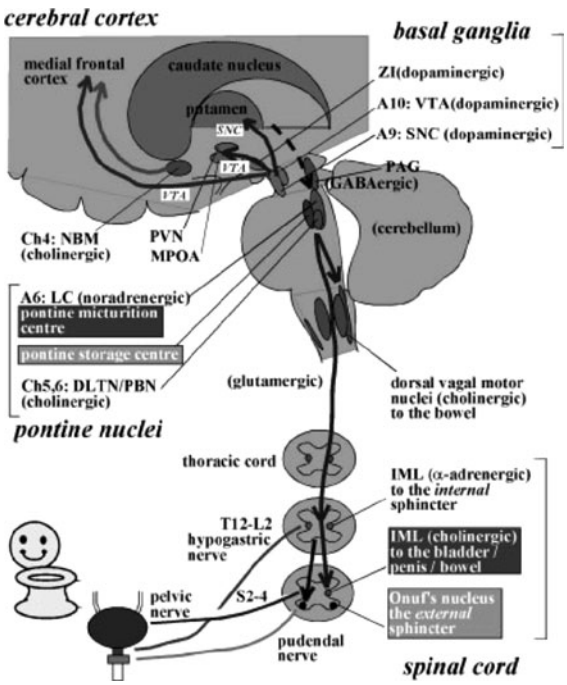
Prevalence

Earlier studies reported that lower urinary tract symptoms affect 38 to 71% of individuals with PD [8–10]. These prevalence rates are unlikely to reflect the true rates as there are difficulties with diagnosis, methodology, the likely inclusion of patients with atypical parkinsonism and the use of medications.

Recent studies have attempted to overcome these difficulties by using accepted diagnostic criteria for PD, thereby excluding other forms of parkinsonism, in particular, MSA which was not originally recognized as a separate entity. In addition, many early study methods used non-validated questionnaires. Using validated questionnaires, the prevalence of urinary disturbances (UD) is between 27 and 64% [6, 11–13]. However, it is clear that patients with PD experience significantly more urinary symptoms than healthy controls [12, 13].

Pathogenesis of voiding dysfunction in PD

Control of the lower urinary tract. *Source* Sakakibara et al. [5]



The neurological control of the bladder is complex, involving coordination of the somatic and autonomic nervous systems to allow safe storage of urine and appropriate and efficient voiding. Neurogenic bladder control involves almost all aspects of the nervous system: suprapontine and pontine function, intact spinal connections between pons and the sacral cord, and intact peripheral nerves [3].

The sympathetic nervous system originates in the thoracolumbar spinal segments, and via the hypogastric nerve functions during bladder filling to maintain closure of the internal urethral sphincter and also inhibits parasympathetic stimulation of the bladder. This allows compliance and distension of the bladder muscle to accommodate urine safely at low pressures.

Efferent parasympathetic innervation to the bladder and urethra originates in the intermedio-lateral column of S2 and S4 segments of the spinal cord and acts via pelvic splanchnic nerves to produce detrusor muscle contraction, relaxation of the urethral smooth muscle and facilitate voiding.

Somatic nerve fibres arising from Onuf's nucleus in the anterior horn of the sacral spinal cord run with the parasympathetic nerves to supply the rhabdosphincter and the pelvic floor muscles.

The pudendal nerve arises from the anterior horn motor neuron cell bodies of S2, S3 and S4 to innervate the urethra and the pelvic floor musculature. It also takes afferent impulses from the urethra relaying sensory information to the brainstem and cerebral cortex.

Blok et al. [14] have used functional brain imaging to confirm those cortical and brainstem areas that are involved in the control of micturition. Two micturition centres exist in the pons, namely the pontine micturition centre (PMC) and the pontine storage centre [14]. The PMC initiates the micturition reflex whilst the role of the pontine storage centre is less well understood although stimulation leads to strong contraction of the pelvic floor muscles and urethra.

The central nervous system ensures that micturition occurs under voluntary control and at a time and place that is socially acceptable.

Additional information about bladder filling is projected to the peri-aqueductal grey (PAG) matter in the pons [14]. The PAG and several areas of the brain (e.g. Limbic system and cerebral cortex) input into the PMC and initiate micturition when appropriate.

Dopaminergic neurons also play a part in the control of normal micturition. Dopaminergic neurons originate in a region of the midbrain known as the ventral tegmental area (VTA), project to the PMC. Dopaminergic D1 receptors are inhibitory, whereas D2 stimulation facilitates micturition [15]. Dopaminergic neurons are abundant in the VTA as well as the substantia nigra pars compacta (SNC).

Although voiding is a function of the peripheral autonomic nervous system and can occur in a reflex fashion via the sacral micturition centre, it is subject to facilitatory and inhibitory impulses from higher neurologic centres. Regulatory micturition centres present in the pontine-mesencephalic reticular formation are influenced by the cerebral cortex, basal ganglia, thalamic nuclei and the anterior vermis of the cerebellum. The effect on micturition of structures functionally related to the extrapyramidal system, such as the globus pallidus, the red nucleus and the substantia nigra, is considered to be inhibitory in nature [16]. On the basis of these experimental and clinical observations, it is assumed that lesions of the basal ganglia may impair detrusor control.

In PD, degenerative loss of pigmented neurons in the substantia nigra leads to selective depletion of dopamine in the striatum. Lesions of basal ganglia, like PD, result in partial or total disconnection of the micturation reflex from the voluntary control resulting in uninhibited detrusor contractions at low bladder volumes.

The most widely accepted theory of pathogenesis is that the basal ganglia inhibits the micturition reflex in the 'normal' situation via D1 receptors, and that cell depletion in the SNC in PD results in loss of this D1-mediated inhibition and consequently detrusor overactivity [4].

The influence of higher centres on micturition is very complex. Voiding can be influenced by the anterior cingulated gyrus, locus ceruleus and the nucleus tegmento lateralis dorsalis [17]. Kitta et al. [18] have demonstrated decreased activation in cortical areas in patients with PD during bladder filling; however, this is also seen with healthy individuals who voluntarily inhibit micturition. This group has demonstrated increased cerebellar activity during detrusor overactivity in patients with PD [18]. Stimulation of the subthalamic nucleus has been shown to reduce activity in the frontal cortex and anterior cingulate cortex and also reduce urinary symptoms and improve urodynamic parameters in patients with PD [3, 19].

Partial involvement of the corticospinal tract may be an integral part of PD [20]. Others have disputed this theory and shown no evidence of interruption of the corticospinal pathways to the limbs in PD, and therefore, it would seem likely that the corticospinal connections to the urethral sphincter are also intact [21]. Andersen and Bradley [20] found prolonged signal transit times in the pelvic nerve pudendal reflex arc in patients with PD and suggested that denervation may occur secondary to central reflex neural dysfunction as a result of recurrent overdistension and infection [20].

Winge et al. [22] have demonstrated that deep brain stimulation of the subthalamic nucleus (STN) improves symptoms scores [22]. However, they failed to show any significant change in urodynamic parameters, whilst Finazzi-Agro et al. [19] demonstrated urodynamic improvements following stimulation [19].

Winge et al. [23] also demonstrated loss of nigrostriatal dopaminergic neurons on single photon emission computed tomography (SPECT) imaging amongst PD patients with UD. The severity of UD correlated with the relative degeneration of the caudate nucleus, a part of the basal ganglia, which receives dopamine-rich innervation from the SNC and VTA [23].

Urinary disturbances in Parkinson's disease

There is limited information regarding the time of appearance of urinary symptoms in PD; however, UD are thought to occur 6 years after the onset of motor symptoms [24].

There is no consensus on the relationship between UD and disease variables such as disease stage or duration. Some studies have shown a link between these disease variables and UD [11, 25, 26] whilst others have not [13, 27]. Interestingly, one group of researchers has reported that the UD are related to the patients' age rather than the disease itself [28].

Studies report that storage symptoms are present in 57–83% of patients, whereas voiding symptoms are seen in 17–27% patients [29].

Nocturia is the most common complaint in >60% patients with PD [13]. Urgency occurs in 33–54% of patients, whilst frequency is experienced by 16–36% of patients [11, 13]. However, it is well known that patients with PD experience sleep disturbance, and therefore, the prevalence of 'true' nocturia would be difficult to determine.

Although voiding symptoms are not as frequent, Sakakibara et al. [1] found that hesitancy, poor flow and straining were seen more often in patients with PD than the control group [1].

Urodynamic observations in Parkinson's disease

Urodynamic studies are a useful tool for investigating those with complicated UD and PD who fail to respond to first-line treatment.

Storage

Detrusor overactivity (DO) is the commonest cystometric abnormality in patients with PD.

The International Continence Society definition of DO is the urodynamic finding of involuntary detrusor

contractions during bladder filling which may be spontaneous or provoked [30]. When it is associated with an underlying neurological condition, it is known as neurological DO, although it may also occur in non-neurological conditions, for instance, bladder outflow obstruction. Distinguishing between the two can be difficult as both conditions may coexist in the same patient; however, it has been found that neurogenic DO tends to be more severe than idiopathic DO as involuntary contractions occur at an earlier stage of bladder filling [27].

The rate of neurogenic DO in patients with PD is 45–93% [9, 10, 17, 31–34].

In one study, 46% of patients with PD had small bladder capacity <200 ml [10] which may contribute to symptoms of frequency that many experience.

Voiding

By contrast, detrusor areflexia, the urodynamic finding of acontractility due to an abnormality of nervous control [30], is an uncommon finding and when present may often be due to anticholinergics. In one study, a weak detrusor was seen in 40% of men and 66% of women [35], and a correlation has been found between a weak detrusor and stage of disease [17]. Araki et al. [33] reported rates of 16% of hyporeflexia or areflexia in his group that included those on anticholinergics [33], whilst Fitzmaurice et al. [32] were unable to demonstrate detrusor areflexia even in those still taking anticholinergic medication [32]. Other studies have failed to elicit detrusor arreflexia after withholding anticholinergics [17]. Detrusor sphincter dyssynergia (DSD) is a rare cause of voiding dysfunction in Parkinson's disease. DSD was observed on voiding at a rate of 0–3% [31, 33–35]. A small number of reports have suggested that infravesical mechanisms, namely external urethral sphincter and pelvic musculature, are involved in UD in PD. In one series, 11% showed sphincter bradykinesia [31] whilst in another series, 37% showed incomplete relaxation of the pelvic floor [17]. This dysfunction of infravesical mechanism results in hesitancy and poor stream and can in turn lead to bladder outflow obstruction with secondary DO, although obstructed voiding patterns are not common in patients with PD [33], and generally patients with PD have low bladder residuals [36]. None had post-void residuals of more than 100 ml [35].

Effect of dopaminergic medication

Patients with PD are likely to have had motor symptoms for a number of years before the onset of urinary symptoms and most will be on anti-parkinsonian medication, including dopaminergic therapy, by the time they present to urologists. These patients may even display 'wearing off' phenomena, periods when the medication does not work, and have various other non-motor symptoms. Clearly, the effect of dopaminergic medication requires consideration in addition to the known effects of PD in causing DO.

Although the motor symptoms of PD respond well to dopaminergic therapy, studies on their effects on bladder function have produced conflicting results.

Dopamine receptor antagonists are generally used in the treatment of new patients, although levodopa has been the mainstay of pharmacological treatment for PD. Levodopa has been shown to have an unpredictable effect on bladder function. A few studies have shown improvement in bladder capacity in those medicated with dopaminergics [37, 38], whereas other studies have found that levodopa decreases DO in some but worsens in others [32, 39]. Christmas et al. [39] pointed out that because their patients were all premedicated with domperidone, a peripheral dopamine antagonist, it follows that the effects on both smooth and striated musculature of the lower urinary tract are mediated by changes in the central dopaminergic transmission. This mechanism of centrally mediated bladder dysfunction is also supported by Brusa et al. [40] who showed that levodopa reduced bladder capacity and worsened DO in patients with early-stage disease [40].

Brusa et al. [41] subsequently studied the acute and chronic effects of levodopa and reported that acute dosing worsened bladder function, whereas chronic administration improved bladder function in terms of volume at first sensation, neurogenic DO contractions threshold. The explanation provided for this is that acute and chronic therapy produces different dopamine synaptic concentrations and thus different activation of D1 and D2 receptors [41].

Uchiyama et al. [42] found that in advanced PD and those affected by on–off phenomenon, levodopa worsened DO during storage but improved detrusor contractility during voiding and therefore improved bladder emptying [42].

Female voiding dysfunction in PD

Few studies have evaluated UD in females with PD. The majority with urinary symptoms (>70%) will manifest symptomatic urgency with or without urge incontinence. The remaining patients will have mixed storage and voiding or pure voiding symptoms. Urodynamic evaluation demonstrates neurogenic DO in 70–80% of female patients [9, 43]. Women with Parkinson-related syndromes demonstrate detrusor hypocontractility or arreflexia in 20–30% of cases. EMG reveals sphincteric dysfunction (pseudodyssynergia, bradykinesia) in 30–50% of patients.

Khan et al. [44] evaluated 17 women with PD, all but one of which had urgency symptoms associated with urge incontinence. The prevalence of hyperreflexia was 70% and genuine stress incontinence 50%. Five of 14 women who underwent coaxial needle EMG were found to have external sphincteric dysfunction. Three women demonstrated hyporeflexic bladder contraction [44].

Gray et al. [28] examined 34 women and 42 men with PD and compared them to 3 groups: women and men with incontinence but no identifiable neurologic disease; patients with cerebrovascular disease; and patients with dementia. Of the women with PD, 79% demonstrated neurogenic DO. Women with PD tended to have lower residual volumes than the other patient groups. Bladder capacity was also reduced compared to age-matched controls and more closely approximated female patients one decade older [28]. Other authors have been unable to identify significant reductions in bladder capacity in males with PD [32, 39]. No significant evidence of outflow obstruction was seen in women with PD using detrusor opening pressure as the discriminant tool.

Aranda and Cramer [37] studied 41 patients of which 17 were female. He demonstrated detrusor hypocontractility in 12% (all women). Female patients experienced significant nocturia, high postvoid residual and dysuria [37].

Investigation of urinary dysfunction in patients with PD

Careful analysis of symptoms including clinical examination, urodynamics and radiographic data is essential before selecting a treatment, especially prostate surgery.

Scoring systems are useful in the screening and severity assessment of symptoms. Studies show that standardized urinary symptom-scoring systems may be helpful although these validated symptom-scoring systems are non-specific and cannot distinguish symptoms due to neurological conditions and BPH [12]. Nevertheless, Araki and Kuno [11] reported that the International Prostate Symptom Score (IPSS) is useful for evaluating the severity and type of bladder dysfunction in PD and that symptom scores can be accurate for predicting likely urodynamic abnormalities [11]. However, the main criticism of the IPSS questionnaire in patients with PD is that it does not address incontinence.

Those with PD and complicated LUTS should undergo full urodynamic investigation including cystometry, sphincter EMG, flowmetry, electromyelography and ultrasonography before treatment is initiated.

Urinary outflow obstruction is difficult to diagnose in PD, but may coexist with DO. Fitzmaurice et al. [32] suggested that those who empty their bladders completely both on and off treatment probably have no evidence of obstruction, despite high maximum detrusor pressures and low flow rates. They disputed Galloway's suggestion that obstruction in PD occurs at the level of the striated sphincter, as their fluoroscopic studies showed normal relaxation of this area both on and off treatment. Furthermore, their EMG analysis showed no evidence of a lower motor neurone lesion affecting the striated urethral sphincter in idiopathic PD [32].

Differentiation between PD and multiple system atrophy

Approximately 50% of MSA is misdiagnosed as having PD [45]. MSA is another neurodegenerative condition that may present with parkinsonism combined with features of cerebellar ataxia and autonomic failure. It is well recognized that patients initially diagnosed with PD may in fact have MSA, and it is important to distinguish the two as their urological management is different.

MSA may be preceded by UD, and therefore, the condition is most likely to be seen by urologists.

At this early stage, neurological symptoms may be subtle.

As in PD, there is also diffuse involvement of several neural systems in MSA. Suprapontine involvement is thought to cause detrusor overactivity whilst atrophy of the efferent parasympathetic tracts may be the cause of incomplete bladder emptying. By contrast, Onuf's nucleus is involved in MSA but spared in PD [46]. Consequently, some authors describe the use of external sphincter EMG to distinguish between the two conditions.

Urinary incontinence is significantly more common (60–100%) [34, 44]. Affected individuals are also more likely to have significant PVR > 100mls compared to patients with PD (66% vs. 16%, respectively). Sakakibara et al. [47] found that 45% of patients with MSA had DSD, which may in part account for the common finding of incomplete bladder emptying with subsequent incontinence. Urinary frequency (33–45%) and urgency (63–67%) are also more common in MSA than PD [34, 47].

Affected individuals carry a worse prognosis including poor response to surgery. Post-operative incontinence rates as high as 100% have been reported following TURP [26].

Urodynamic abnormalities may aid differentiation between MSA and PD. Berger et al. [48] observed an open bladder neck at rest on voiding cystourethrogram which was not seen in patients with PD except those who had undergone prostatectomy [48]. Stocchi et al. [17] found sphincter electromyography (EMG) provides important differentiating data between MSA and PD with sphincter dysfunction more prominent in MSA [17].

Only medical management should be offered if MSA is suspected: anticholinergics for DO, intermittent self-catheterization (ISC) for high post-void residual (PVR) and desmopressin for nocturnal frequency. Alpha-blockers should be avoided in MSA as they can exacerbate postural hypotension.

Treatment for urinary tract dysfunction in patients with PD

It is important to exclude or treat urinary tract infection in patients who have LUTS. Simple measures like fluid management, with adjustment of the volume, timing and type of fluid intake, should also be used in conjunction with pharmacotherapy.

Anticholinergic medications

Storage symptoms of PD may respond to anticholinergics; however, no randomized controlled trials of anticholinergics have been undertaken specifically in this group of patients.

Anticholinergics act via the effect on the parasympathetic system, specifically on the M3-receptors in the bladder. The potential benefit of these drugs should be balanced with potential adverse side effects especially in elderly patients. Winge and Fowler [3] have recommended a practical algorithm to manage patients with PD with detrusor overactivity, the cornerstone of management being the use of anticholinergics and estimation of post-void residuals (Fig. 1) [3].

If therapy with a single agent proves to be unsuccessful, the tricyclic antidepressant imipramine can be used in combination with the above-mentioned drugs due to different receptor sites for their mechanism of action [49].

If anticholinergics fail to reduce symptoms of frequency and urgency, the patient should be seen by a nurse Continence Advisor for advice about appliances to help with containment [50].

Voiding symptoms

Management of voiding symptoms should begin with a careful history, searching for medications with an anticholinergic effect.

Urodynamic evaluation will detect significant bladder outflow obstruction with or without DO. Surgery for documented bladder outlet obstruction is advised in patients with PD although a trial of medical therapy (alpha blocker and/or 5-alpha reductase inhibitor) may be a reasonable first option [50]. The patient should understand that such surgery is primarily indicated for the relief of obstruction and to avoid catheterization [34], but may not resolve the coexistent storage symptoms. Sotolongo [49] showed that detrusor instability could be improved in 60–70% of patients post-operatively if it was the result of prostatic obstruction [49].

The risk of de novo incontinence arising after transurethral prostatectomy in a parkinsonian patient

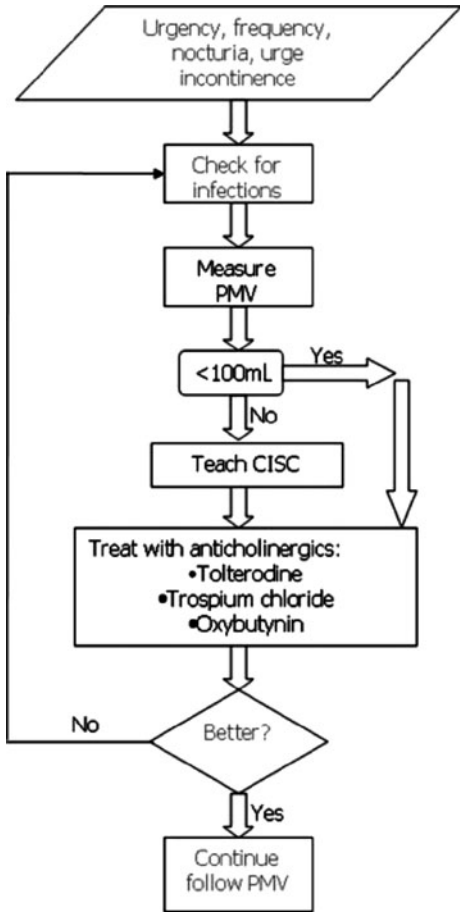


Fig. 1 Practical algorithm for the management of patients with symptoms of detrusor over-activity (DO) [11]

is approximately 20%. This risk is much higher than the risk of approximately 1% for the general population. However, the incontinence risk in a continent parkinsonian patient with normal voluntary sphincter control is approximately 4%, whilst the comparable risk in a parkinsonian patient with abnormal voluntary sphincter control is approximately 83%. The reasons for the association between loss of voluntary sphincter control and incontinence are not completely clear. It has been shown that complete paralysis of the external sphincter does not produce incontinence in the otherwise normal patient following transurethral prostatectomy [51]. Thus, other factors must be implicated, such as the concomitant presence of DO occurring in Parkinsonism that does not abate after prostatectomy. Urinary incontinence is likely and it should be expected in patients with absent or poor voluntary sphincter control preoperatively. In this group, non-operative means of management (for example, clean intermittent catheterization) might be recommended whenever feasible. If an operation is required, the high risk of incontinence should be communicated to the patient. In contrast, parkinsonian patients with normal voluntary sphincter control suffer a risk of incontinence that approximates that in the non-parkinsonian population. Indeed, patients who are incontinent preoperatively may become continent after transurethral prostatectomy if they demonstrate normal voluntary sphincter control. However, no incontinent patient with abnormal voluntary sphincter control became continent post-operatively. Nevertheless, an operation may be indicated in this group to relieve outflow obstruction even though the continence status will probably remain the same.

Other treatments

Diazepam, baclofen or dantrolene may be useful in relaxing striated muscle in patients with hyper-reflexic external sphincters. Serotinergic neurons centrally facilitate urine storage, and the use of serotonergic drugs such as duloxetine may be used to treat bladder overactivity in PD [52].

Nocturnal polyuria is common in the elderly and those with PD. The loss of the normal circadian vasopressin rhythm has been demonstrated in experimentally-produced parkinsonism [53]. It should be distinguished from DO with the use of a bladder diary. Desmopressin has been shown to be effective in reducing nocturia in patients with PD. Fowler [50], however, contends that this agent should be avoided because of the risk of hyponatremia aggravating confusional states [50]. This medication should therefore be used with extreme caution for nocturia in PD.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) may be useful in patients with PD. The STN is considered a key area in the PD, and stimulation leads to inhibition of the micturition cycle [4]. DBS leads to decrease in urinary symptoms in PD [22] but conflicting effects on the urodynamic parameters. Some studies suggest increased bladder capacity and increase in volume at first desire whilst others show no change in urodynamic profile [3, 19].

Nerve stimulation studies

Neuromodulation is widely described as a treatment for detrusor overactivity; however, there is little research on the use of this technique of treatment in neurogenic detrusor overactivity seen in patients specifically with PD.

The mechanism of action of neuromodulation is unknown although it is thought that it probably causes rebalancing of inhibitory and excitatory impulses that control bladder function in the central nervous system.

Sacral nerve modulation is one method described by Wallace et al. [54] in the treatment of neurogenic bladders. Their results show that 85% of patients have a successful test stimulation trial (>50% reduction in leakage episodes, nocturnal or pad usage over a 1–3 week period) with subsequent implantation of the pulse generator. Sacral stimulation resulted in an average 68% decrease in incontinence episodes (from 4 to 1.3 per 24 h) and night-time voids (from 2.6 to 0.8 per night), and a 72% reduction in the number of pads used per 24 h (from 3.5 to 1.0). In their series, 6 out of 33 of their patients had PD. These results suggest that sacral nerve stimulation may have short-term efficacy in patients with underlying neurologic disease who have had successful test stimulation. However, as the authors noted, long-term efficacy of sacral nerve neuromodulation in these patients needs further research because neurologic diseases, such as multiple sclerosis and PD, are typically progressive and hence may have variable responses over time. Thus, longer follow-up in a larger number of patients is needed.

Another method described in patients with PD involves stimulation of the posterior tibial nerve PTNS [55]. Kabay et al. [55] conclude that PTNS produces significant improvements in urodynamics parameters; there is an acute effect of DO suppression and relief of pseudodysynergia as well as improved bladder capacity; however, the investigators also state that the results should be verified in a prospective multicentre study.

Future treatment perspectives

Studies to evaluate the role of neurotransplantation (cellular therapies such as foetal cell implantation) will be important.

References

1. Sakakibara R, Shinotoh H, Uchiyama T et al (2001) Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci 92(1–2):76–85
2. National Collaborating Centre for Chronic Conditions (2006) Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. Royal College of Physicians, London
3. Winge K, Fowler CJ (2006) Bladder dysfunction in parkinsonism: mechanisms, prevalence, symptoms, and management. Mov Disord 21(6):737–745
4. Blackett H, Walker R, Wood B (2009) Urinary dysfunction in Parkinson's disease: a review. Parkinsonism Relat Disord 15:81–87
5. Sakakibara R, Uchiyama T, Yamanishi T et al (2010) Review: genitourinary dysfunction in Parkinson's disease. Mov Disord 25(1):2–12
6. Barone P, Antonini A, Colosimo C et al (2009) The Priamo study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 24(11):1641–1649
7. Braak H, Ghebremedhin E, Rub U et al (2004) Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 318:121–134
8. Andersen JT (1958) Disturbances of bladder and urethral function in Parkinson's disease. Int Urol Nephrol 17:35–41
9. Murhaghan GF (1961) Neurogenic disorders of the bladder in Parkinsonism. Br J Urol 33:403–409
10. Hattori T, Yasuda K, Kita K et al (1992) Voiding dysfunction in Parkinson's disease. Jpn J Psychiatry Neurol 46(1):181–186
11. Araki I, Kuno S (2000) Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry 68(4):429–433
12. Lemack GE, Dewey RB, Roehrborn CG et al (2000) Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. Urology 56:250–254
13. Campos-Sousa RN, Quagliato E, da Silva BB et al (2003) Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr 61(2B):359–363
14. Blok BF, Holstege G (1994) Direct projections from the peri-aqueductal grey matter to the pontine micturition centre M-region. An antegrade and retrograde tracing study in the cat. Neurosci Lett 166:93–96
15. Hashimoto K, Oyama T, Sugiyama T et al (2003) Neuronal excitation in the ventral tegmental area modulates the micturition reflex mediated via the dopamine D(1) and D(2) receptors in rats. J Pharmacol Sci 92:143–148
16. Ruch TC (1974) The urinary bladder. In: Ruch TC, Patton HD (eds) Physiology and biophysics: circulation, respiration and fluid balance, vol 2. W. B. Saunders Co, Philadelphia, pp 525–546
17. Stocchi F, Carbone A, Inghilleri M (1997) Urodynamic and neurophysiological evaluation of Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 62(5):507–511
18. Kitta T, Kakizaki H, Furuno T et al (2006) Brain activation during detrusor overactivity in patients with Parkinson's

disease: a positron emission tomography study. J Urol 175(3 Pt 1):994–998
19. Finazzi-Agro E, Peppe A, d'Amico A et al (2003) Effects of subthalamic nucleus stimulation on urodynamic findings in patients with Parkinson's disease. J Urol 169:1388–1391
20. Andersen JT, Bradley WE (1976) Cystometric, sphincter and electromyelographic abnormalities in Parkinson's disease. J Urol 116:75–78
21. Dick JPR, Cowan JMA, Day BL (1984) The corticomotoneurone connection is normal in Parkinson's disease. Nature 310:407–409
22. Winge K, Nielsen KK, Stimpel H et al (2007) Lower urinary tract symptoms and bladder control in advanced Parkinson's disease: effects of deep brain stimulation in the subthalamic nucleus. Mov Disord 22(2):220–225
23. Winge K, Friberg L, Werdelin L et al (2005) Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. Eur J Neurol 12:842–850
24. Bonnet AM et al (1997) Urinary disturbances in striatonigral degeneration and Parkinson's disease: clinical and urodynamic aspects. Mov Disord 12(4):509–513
25. Winge K, Skau A, Stimpel H et al (2006) Prevalence of bladder dysfunction in Parkinson's disease. Neurourol Urodyn 25:116–122
26. Chandiramani VA, Palace J, Fowler CJ (1997) How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol 80:100–104
27. Defrietas GA, Lemack GE, Zimmern PE et al (2003) Distinguishing neurogenic from non-neurogenic detrusor overactivity: a urodynamic assessment of lower urinary tract symptoms in patients with and without Parkinson's Disease. Urology 63:651–655
28. Gray R, Stern G, Malone-Lee J (1995) Lower urinary tract dysfunction in Parkinson's disease: changes related to age and not disease. Age Ageing 24(6):499–504
29. Singer C (2007) Urological dysfunction. Vol II in Parkinson's disease and nonmotor dysfunction. Humana Press, Totowa, pp 139–148
30. Abrams P, Cardozo L, Fall M et al (2002) Standardisation sub-committee of the international continence society. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. Neurourol Urodyn 21(2):167–178
31. Pavlakis AJ, Siroky MB, Goldstein I et al (1983) Neurologic findings in Parkinson's disease. J Urol 129:80–83
32. Fitzmaurice H, Fowler CJ, Rickards D et al (1985) Micturition disturbance in Parkinson's disease. Br J Urol 57:652–656
33. Araki I, Kitahara M, Oida T et al (2000) Voiding dysfunction and Parkinson's disease: urodynamic abnormalities and urinary symptoms. J Urol 164:1640–1643
34. Berger Y, Blaivas JG, de la Rocha ER et al (1987) Urodynamic findings in Parkinson's disease. J Urol 138(4):836–838
35. Sakakibara R, Hattori T, Uchiyama T et al (2001) Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 71:600–606
36. Winge K, Stimpel H, Nielsen KK et al (2005) Prevalence of bladder dysfunction in Parkinson's disease. Mov Disord 20(Suppl 10):102
37. Aranda B, Cramer P (1993) Effect of apomorphine and L-dopa on the parkinsonian bladder. Neurourol Urodyn 12(3):203–209
38. Winge K, Werdelin LM, Nielsen KK et al (2004) Effects of dopaminergic treatment on bladder function in Parkinson's disease. Neurourol Urodyn 23:689–696
39. Christmas TJ, Chapple CR, Lees AJ et al (1988) Role of apomorphine in parkinsonian voiding dysfunction. Lancet 8626–8627:1451–1453
40. Brusa L, Petta F, Pisani A et al (2006) Central acute D2 stimulation worsens bladder function in patients with mild Parkinson's disease. J Urol 175(1):202–207
41. Brusa L, Petta F, Pisani A et al (2007) Acute vs chronic effects of L-dopa on bladder function in patients with mild Parkinson's disease. Neurology 68:1455–1459
42. Uchiyama T, Sakakibara R, Hattori T et al (2003) Short-term effect of a single levopdopa dose on micturition disturbance in Parkinson's disease with the wearing off phenomenon. Mov Disord 18(5):573–578
43. Porter RW, Bors E (1971) Neurogenic bladder in parkinsonism: effect of thalamotomy. J Neurosurg 34:27–32
44. Khan Z, Starer P, Bhola A (1989) Urinary incontinence in female Parkinson disease patients: pitfalls of diagnosis. Urology 33:486–489
45. Quinn N (1995) Parkinsonism–Recognition and differential diagnosis. Br Med J 310:447–452
46. Kirchhof K, Apostolidis AN, Mathias CJ et al (2003) Erectile and urinary dysfunction may be the presenting features in patients with multiple system atrophy: a retrospective study. Int J Impot Res 15:293–298
47. Sakakibara R, Hattori T, Uchiyama T (2000) Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? J Neurol Neurosurg Psychiatry 68:65–69
48. Berger Y, Salinas JM, Blaivas JG (1990) Urodynamic differentiation of Parkinson disease and the Shy-Drager syndrome. Neurourol Urodyn 9:117–121
49. Sotolongo JR (1988) Voiding dysfunction in Parkinson's disease. Semin Neurol 8(2):166–169
50. Fowler CJ (2007) Update on the neurology of Parkinson's disease. Neurourol Urodyn 26:103–109
51. Krahn HP, Morales PA (1965) The effect of pudendal nerve anaesthesia on urinary continence after prostatectomy. J Urol 94:282
52. Andersson KE (2000) Treatment of overactive bladder: other drug mechanisms. Urology 55:51–57
53. Hineno T, Mizobuchi M, Hiratani K et al (1992) Disappearance of circadian rhythms in Parkinson's disease model induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine in dogs. Brain Res 580:92–99
54. Wallace PA, Lane FL, Noblett KL (2007) Sacral nerve neuromodulation in patients with underlying neurologic disease. Am J Obstet Gynecol 197:96.e1–96.e5
55. Kabay SC, Yucel M, Ozden H (2009) Acute urodynamic effects of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. Neurourol Urodyn 28:62–67