NEUROGENIC INCONTINENCE

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Sidra is a third-year medical student studying at Lancaster University. Neurology has always held a special interest for her and in this article she writes on the topic of urinary incontinence from a neurological point of view, looking at the treatment modalities for neurogenic urinary incontinence, focusing particularly on botox and neuromodulation.

INTRODUCTION

Urinary incontinence is defined by the International Continence Society (ICS) as 'the complaint of any involuntary leakage of urine.' It may be a 'symptom, a sign, or a condition [see table 1], but it is a non-specific diagnosis and fails to identify the underlying pathophysiologic process.'[1] Urinary continence is necessary before social integration is possible in our civilisation today, implying functional reliability of the entire urinary tract.[1] The prevalence of urinary incontinence has been estimated at 2-20%,[2] with incidence increasing with age.[3]

Stress

- inadequate pelvic support with urethral hypermobility
- inadequate sphincter closure due to anatomic defect or functional impairment
- lower motor neuron injury
- retention
- low compliance
- pharmacologic agents (adrenergic antagonists)

Urge

- detrusor overactivity
  - idiopathic
  - neurogenic (upper motor neuron involvement)
  - continuous
- fistula
- ectopic ureter
- severe stress incontinence or low compliance

Table 1 Types of urinary incontinence – symptoms and associated conditions[4]

THE URINARY BLADDER

The bladder is a muscular organ located in the pelvis when empty and expanding into the abdominal cavity as it fills. The trigone is a specialised area of the bladder base extending from the two ureteric orifices to the internal urethral meatus.[5] The bladder neck in females is associated with endopelvic fascia, pubovesical ligaments with smooth muscle continuing obliquely or longitudinally into the urethral wall.[5] The detrusor muscle, bladder neck, and striated external sphincter function as a synergistic unit for adequate storage and complete evacuation of urine, receiving a rich supply of cholinergic fibres.[5]

The bladder's essential function is to store urine at low pressures and periodically eliminate liquid waste. It acts as a reservoir with a capacity ranging between 400-500ml and is typically emptied 5-7 times/day.[4] The bladder is a dynamic organ that can respond to increased filling, infection, or even emotional stimuli.[4]

PATHOPHYSIOLOGY OF THE NEUROGENIC BLADDER

Neurogenic bladder dysfunction (NBD) is a functional disturbance that can develop as a result of a lesion at any level in the nervous system (see table 2). Conditions in children leading to NBD are predominantly congenital neural tube defects. Acquired causes such as spinal cord tumours, trauma, transverse myelitis,[5] sacral agenesis or iatrogenic injury[2] are less frequent. Myelomeningocele patients may present with neurogenic sphincteric dysfunction due to incompetent smooth muscle contribution to the bladder neck.[2,8] In adults, neurogenic bladders may follow stroke, Alzheimer's disease, multi-infarct dementia, other dementias and Parkinson's disease.[7]

According to the standardisation of terminology published by the ICS in 2002, detrusor overactivity (DO) is a 'urodynamic observation characterised by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked.'[9] It is subdivided into neurogenic detrusor overactivity (NDO) when there is an established neurological cause or idiopathic detrusor overactivity when no known cause for the overactivity is present (see table 1).[3] The ICS defines overactive bladder (OAB) as a 'symptom complex described as urgency, with or without urge incontinence, usually with frequency and nocturia'[9] in the absence of local pathological or hormonal factors.[3] Patients with OAB syndrome are often treated without a urodynamic confirmation of the underlying diagnosis, often found to be DO.[3]

Disordered innervation of the detrusor musculature and external sphincter adversely affect bladder function.[5] As detrusor pressure increases, glomerular filtration rate (GFR) decreases causing deterioration of pyelocaliceal and ureteral drainage, leading to obstructive hydronephrosis and/or vesicoureteral reflux (VUR). Even if VUR or upper urinary tract (UUT) dilatation is absent, high intravesical pressure can impair drainage of urine into the bladder.[5]

Detrusor hypertonia or hyperreflexia can result in intermittent elevation of bladder pressure. Detrusor hyperreflexia elevates pressures especially if the external sphincter acts reflexively and tightens rather than relaxes in an attempt to prevent micturition (detrusor sphincter dyssynergia (DSD)).[5] Detrusor hypertonia or small-capacity hypertrophic bladder secondary to outflow obstruction can lead to

Site of lesion	Aetiology	Effects on Bladder function	Effects on Sphincter
Suprapontine	○ Parkinson's disease ○ stroke ○ dementia	detrusor hyperreflexia	normal
Suprasacral	○ spina bifida ○ tumours ○ spinal cord injury ○ multiple sclerosis	detrusor hyperreflexia	external sphincter dyssynergia
Sacral	○ sacralagenesis ○ tumours	detrusor areflexia (acontractility) or detrusor hyperreflexia	IDSO* or DSD**
Peripheral	○ spina bifida ○ tumours ○ spinal cord injury ○ multiple sclerosis ○ diabetes	detrusor areflexia – low pressure or poorly compliant	IDSO*
* = isolated distal sphincter obstruction ** = detrusor sphincter dyssynergia			

Table 2 Types of neuropathic bladder dysfunction[6]

continuous elevation.[5] Bladder outlet obstruction is caused by DSD or fibrosis of the external urethral sphincter. Recurrent urinary tract infections (UTI) due to bladder residue may lead to transmural inflammation and fibrosis.[5] Any pathophysiologic process that causes either intermittent or continuous elevation of bladder pressure above 40cm H_2O can cause episodes of acute pyelonephritis and irreversible renal damage.[5]

MANAGEMENT

Individuals with neurogenic bladders are some of the most challenging patients to manage. Not only does their bladder dysfunction arise in conjunction with a range of underlying conditions (eg, multiple schlerosis (MS), Parkinsonism), but within each condition the severity and clinical characteristics can vary widely.[10] Hence, management largely needs to be considered on an individual basis (see figure 1). The treatment goals for NBD are to preserve renal function by reducing detrusor pressure (ie, <40cm H_2O) and to improve quality of life by preventing incontinence episodes.[10] The correction of incontinence is a therapeutic challenge due to the unavoidable deterioration of bladder function in cases of neurogenic bladder, the complexity and gradual evolution of the underlying pathology and the multiplicity of treatments available.[1] The involvement of many different specialties in the management of such patients (eg, neurology, rehabilitation, pain management, urology and gynaecology) each having its own primary goal of treatment, complicates management further.[11]

MEDICAL MANAGEMENT

The introduction of clean intermittent catheterisation (CIC) in the 1970s[12] revolutionised the management of neuropathic lower urinary tract dysfunction and is now considered the 'gold standard' approach. However, this strategy of bladder management can be difficult for patients with poor upper extremity dexterity, eyesight and DSD.[12] Patients with extensive urethral damage or with progression of their disease are appropriate candidates for alternate management options. For spinal cord injured (SCI) patients who are unable or unwilling to participate in a CIC program, suprapubic catheters (SPC) are an appropriate second-line option.[12]

Oral anticholinergic agents have been widely used as first-line treatment for patients with neurogenic bladders, oxybutynin being the most commonly used. However, some patients may not respond or may experience troublesome systemic side effects such as dry mouth, constipation, facial flushing, dizziness[13] and blurred vision. Intravesical treatments may provide alternatives to improve effectiveness, avoid high systemic drug levels and minimise undesired anticholinergic side effects.[12] Trans-cutaneous use of oxybutynin is another way of delivering the drug.[13]

A recent study carried out a systematic literature review of eight studies, looking at a total of 297 children with neurogenic bladders who were given intravesical oxybutynin.[13] In general, a marked improvement in urinary incontinence was reported, with most studies having high 'dry and improved' rates.[13] Neurogenic detrusor overactivity improved from 33% to 77%. This improvement may be a result of the antimuscarinic action on the cholinergic receptors and the local analgesic effect on the sensitive C fibre afferents in the detrusor.[13] Anticholinergics work by partially blocking the efferent parasympathetic innervation of the detrusor thus inhibiting involuntary bladder contractions.[13] Although the optimum dose for intravesical instillation has not been determined, most studies in this review used 0.2mg/kg daily.[13]

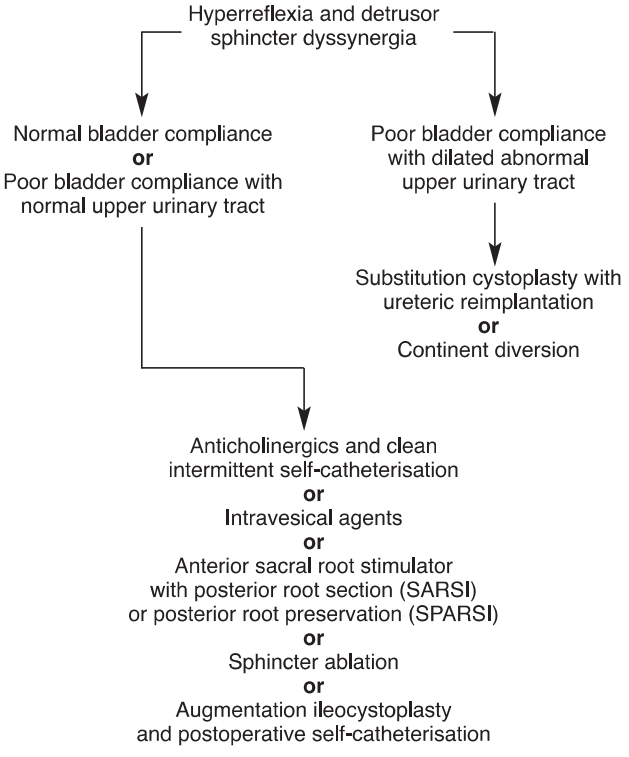
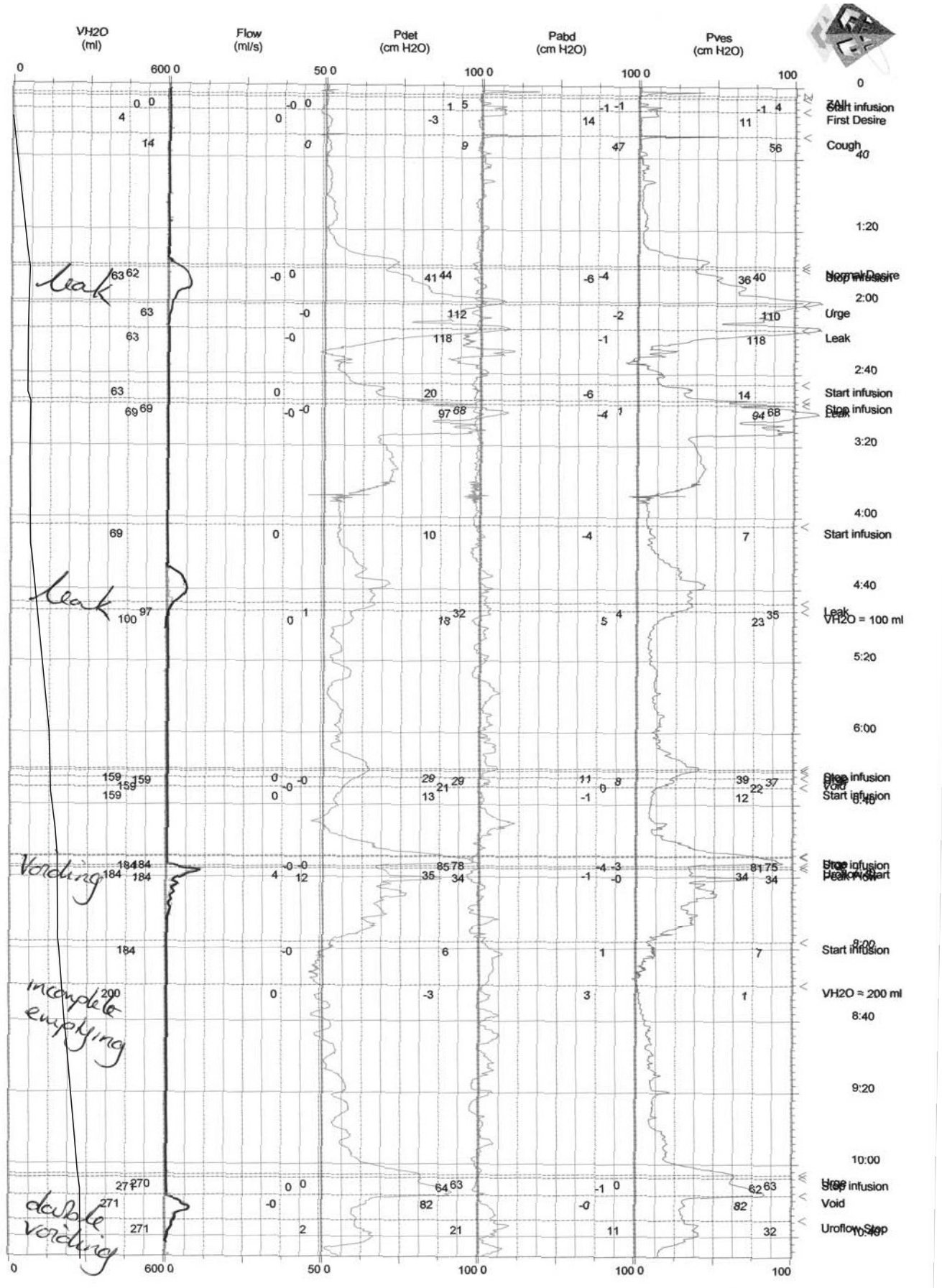


Figure 1 An algorithm for the management of neuropathic bladder dysfunction[8]



Cystometrogram in a case of detrusor hyperreflexia. Columns from left to right show volume of voided urine (VH2O), flow, detrusor pressure (Pdet), abdominal pressure (Pabd) and bladder pressure (Pves). Clinical events are annotated to the left of the page and in this case include leakage of urine and double voiding to attain bladder emptying. (Courtesy of Fiona Sexton, clinical nurse specialist in urology)

Various studies showed the effects on urinary incontinence after treatment with intravesical oxybutynin. Length of treatment ranged from three to 36 months across the studies[16] and study samples were small, ranging from six patients to 29 patients. Four studies showed continence was achieved in >50% of their patients. Improvement in incontinence symptoms, eg reduction in pads, dry during the day, was seen in 17-30% of patients in small study samples (six, ten and 13 patients respectively) and 66% in a study of 29 patients.

Avoiding the oral route with drug absorption via the portal venous system decreases side effects but even when oxybutynin is administered intravesically side effects are still possible, probably secondary to drug absorption through the bladder mucosa.[13]

This series of studies was large enough to show evidence-based results but included a heterogeneous population, which could bias and threaten the external validity of the conclusions. Restricting the inclusion criteria to age less than 18 years may have precluded a more comprehensive assessment of this treatment, and adding adults could have enriched the results.[13]

Botulinum toxin (botox) A intradetrusor injections were introduced in 2000 as a minimally invasive second-line treatment option for NDO for patients who are unresponsive to conventional treatment and who are on or willing and able to perform CIC but do not want invasive reconstructive surgery, or are unfit for major surgery.[9,14] Botox, first isolated by van Ermengem in 1897, is a potent neurotoxin produced by the gram-positive anaerobic bacterium *Clostridium botulinum*.[9] It works at neuromuscular junctions by inhibiting acetylcholine neurotransmitter release resulting in striated muscle relaxation.[9] To date, numerous studies have been published on the results of botox injections to treat NDO. Although many of the studies included a small number of patients, overwhelming evidence supports the efficacy, safety, and tolerability of the botulinum toxins, specifically serotype A, over a longterm follow-up without inducing any systemic side effects and allow patients to avoid anticholinergic drug use.[9] Studies show botox has a fast onset of action with significant effects reached within 1-2 weeks, with effects lasting for approximately 8-9 months.[9]

From a systematic literature review of 18 articles it can be concluded that intradetrusor botox injections in adults with NDO, urinary incontinence or other neurogenic overactive bladders (NOAB) symptoms, has beneficial effects both on clinical and urodynamic variables.[9] Complete continence was achieved in approximately 40-80% of patients and mean pDetMax was reduced to <40cm H_2O.[14] There was a simultaneous improvement in all urodynamic parameters and significant reductions in daily frequency of catheterisations and maximum detrusor pressure.[9] A significant increase in maximum cystometric capacity, first volume of uninhibited detrusor contractions and bladder compliance was also noted. During follow-up, these findings remained unchanged. In addition, daytime frequency, nocturia and number of pads used decreased considerably and urinary continence was restored.[9]

The most commonly used dose of botox is 300 units. It was found that doses of 200 and 300 units induced significant decreases in incontinence episodes and improved urodynamics and quality of life (QoL), suggesting that lower doses can also be used.[14] However, optimal doses could not be determined as these studies weren't powered to detect significant differences between the doses.[9]

A study of 16 SCI patients with a six-year follow-up investigated modifications in QoL using a domain-specific questionnaire for urinary incontinence.[14] A dramatic improvement in QoL, correlated with a decrease in the frequency of leakage episodes and of catheterisations, was seen four months after the first injection. This was maintained throughout all follow-up evaluations, indicating a strong association between the clinical success of treatment and improved QoL.[9] Similar results were reported in a randomised, double-blind, multicentre study limited to a 24-week follow-up.[14]

Botox can be injected using any type of anaesthesia; the type used is the choice of the patient and the surgeon. In most studies, botox is injected directly into the detrusor, sparing the trigone due to VUR risk; reportedly, this is still the reference location.[9] However, results of a study on 21 refractory NDO patients confirmed that botox-A injection into the trigone is safe, in terms of the possibility of causing VUR, indicating that the adrenergic control of the trigone's smooth muscle is not affected by botox-A.[15]

The most frequent side effects of botox are injection site pain, procedure-related UTI, and mild haematuria.[9] Muscle weakness and vision disturbances have occurred in a few patients. Treating neurogenic bladders with botox is a balancing act between giving enough to suppress bladder spasticity and prevent urine retention.[16] Additional sphincter injections of low doses of botox-A are recommended to reduce the risk of these complications.[16] As potentially life-long repeated botox injections would be required in 1-10 monthly intervals studies have been conducted to reveal risks of repeated botox injections, concluding the development of resistance due to antibody formation was a major concern.[16] Recently, patients with botox-A resistant NDO were successfully treated with botox-B injections into the detrusor.[16] Switching between botox subtypes seems to be of questionable value considering the need for longterm relief of DO, but needs more studying. Additionally, the longterm effects of denervating the detrusor by botox are largely unknown. Pathological innervation may be enhanced in these patients and lead not only to tolerance but exacerbation of lower urinary tract symptoms.[17] However, there is no evidence from the last 20 years of botox usage in other conditions to suggest that this is the case, but longterm studies specifically assessing these issues are not available.[17]

To improve the future application of botox further research should focus on assessing the optimal dose of botox[9] and whether lower doses will have the same benefits whilst avoiding the need for CIC.[17] To adequately assess the incidence of side effects of botox, future studies need to put effort into adequate documenting and reporting of local and systemic side effects.[9]

SURGICAL MANAGEMENT

Various surgical options exist for neurogenic urinary incontinence resistant to medical therapy. However, surgery is only considered when conservative treatment has failed or wasn't tolerated and use of self-catheterisation is a prerequisite for such patients.[18] A retrospective review on outcomes after surgical management of urinary incontinence

in children with neurogenic incompetence[2] illustrated continence rates were 76-93% after artificial urinary sphincter placement (n=578), 5-63% after bladder neck injection (n=105), 40-100% after bladder neck slings (n=134), and 80% after bladder neck suspension (n=68).[2] These findings suggest that bladder neck closure is a safe and effective method of achieving urinary continence.[2]

Artificial Urinary Sphincter (AUS)

The AUS continues to be the first choice of treatment to increase outlet resistance for all patients who void spontaneously or wish to catheterise per urethra.[19] The AUS will continue to function without revision ten years after implantation and yields the best results when implanted on a virgin bladder neck as tissue erosions are extremely rare.[19]

Slings and Bladder Augmentation

Slings have gained popularity as an alternative to AUS to compress an incompetent bladder outlet for paediatric neurogenic incontinence.[20] A 2007 study looked at 30 patients with neurogenic incontinence that underwent tight 360-degree fascial sling wrap around the bladder neck and appendicovesicostomy without augmentation.[20] It was demonstrated that enterocystoplasty was rarely needed with slings for outlet incompetence,[20] as enterocystoplasty entails a number of risks, including rupture and malignancy, which are potentially life threatening. Review of cases up to 1996 found that 70% of published cases included enterocystoplasty. Similarly, 95% of 162 patients undergoing slings in four studies also underwent augmentation.[20] Reasons for enterocystoplasty during sling placement include presumed inadequate bladder capacity and concern for development of high intravesical pressure from increasing outlet resistance.[20]

A continuous follow-up is required after sling surgery, and reserve augmentation may be needed as a secondary procedure in patients for whom sling surgery was unsuccessful. When the bladder requires augmentation, some form of enterocystoplasty should be performed.[20] Uterocystoplasty should rarely be needed as regular surveillance should prevent ureteral dilatation to the degree needed for a ureterocystoplasty.[19] Whether to use the ileum or colon is the surgeon's choice; the sigmoid colon is used most commonly as it is anatomically convenient.[19]

Incontinent patients with neurologic injuries and catheter-induced urethral destruction can also be treated by urethral closure and ileovesicostomy.[21] A retrospective database review on 50 adults post-ileovesicostomy concluded that ileovesicostomy was a valuable longterm management strategy providing an effective low-pressure conduit for urinary drainage.[22] Tension-free vaginal tapes can also be used to treat urodynamic stress incontinence in females with neuropathic bladders.[23]

NEUROMODULATION

In 1878, Saxtorph reported intravesical electrostimulation in patients with an acontractile bladder. Since then, electrical currents have been used in urology; particularly in the bladder, the pelvic floor muscles and the sacral roots.[24] Brindley developed an electrode for longterm stimulation of spinal roots with the first implant in 1972.[24] Later, Tanagho and Schmidt demonstrated that the stimulation of sacral root S3 modulates detrusor and sphincter action.[24] In October 1997, following two decades of experimentation with sacral root stimulation, sacral neuromodulation (SNS) was approved by America's Food and Drug Administration for treatment of UTIs. More than 25,000 patients have undergone SNS since then.[24]

Reflex pathways concerned in the filling and evacuation phase of the micturition cycle is stimulated by afferent nerve fibres.[24] The suppression of DO can occur by direct inhibition of bladder preganglionic neurons or inhibition of interneuronal transmission in the afferent limb of the micturition reflex.[24] Recent positron emission tomography (PET) studies have shown that activity in the paraventricular gray, involved in activation or inhibition of the micturition reflex at the brain level, can be enhanced or reduced by SNS.[24]

After years of experimental therapy, initiated by Tanagho and Schmidt, SNS is nowadays a widely used therapy.[24] During the last few years, physicians have applied SNS therapy to neurogenic patients reporting inconsistent degrees of positive outcomes (see table 3) in 1/15 patients and in 9/23 patients.[25] Patients not responding to SNS, especially those with incomplete lesions, represent clinical challenges for physicians, for whom only major surgical options are available. Sacral anterior root stimulation is also not an option.[25] Due to the less invasive technique and other technical improvements it is expected that complication rates will further decrease within the coming years.[25]

Six studies illustrate the effect of SNS therapy on neurogenic patients.[24] Four studies, sample sizes ranging from 21 patients to 41 patients, demonstrated 43-76% of patients had a greater than 50% improvement in their symptoms.[24] Similarly, a study of 149 patients showed 59.7% had such an improvement. However, this study measured good result or insufficient result.[24] Therefore, data on patients with >50% improvement are not available and are estimates.[24]

As the pudendal nerve is one of the major nerves innervating the pelvic floor muscles, the external urethral and anal sphincters and the pelvic organs, there have been several attempts to stimulate this nerve, all aimed at achieving a beneficial effect on multiple impaired pelvic functions.[26] This preliminary work represented the basis for a new minimally invasive approach of chronic pudendal nerve stimulation (CPNS) to treat neurogenic patients. CPNS is a reversible therapeutic option offering preliminary reliable screening of patients, allowing a screening phase to evaluate the clinical efficacy.[26] Due to the particular anatomy of the Alcock's canal, surgical exposure of the nerve is difficult and may damage the nerve itself.[25] The procedure is performed to place a tined lead using neurophysiological guidance allowing access to the pudendal nerve through either the perineal or dorsal approach, under local anesthesia.[26] Pudendal nerve stimulation allows activation of pudendal afferents from all three sacral segments together with activation of efferents innervating the external urethral sphincter and pelvic floor muscles.[25]

Electrical stimulation of the dorsal penile/clitoral nerve (DPN) with surface electrodes is an alternative non-destructive treatment option shown to suppress detrusor contractions and increase bladder capacity in SCI and MS patients.[25] However, longterm use of surface electrodes in the genital region may not be well tolerated and result in hygienic

Year	Study Details	Study Population	Results
1999	Randomised multi-centre trial study – SNS therapy for urinary incontinence	34 patients were implanted and received chronic **stimulation** for six months, after which they completed a therapy evaluation test (on *vs.* off). 42 patients in a **delay** group were treated with standard medical therapy for six months and were offered implantation after this period.	After six months, the number of daily incontinence episodes, the number of daily replaced diapers and the severity of incontinence was significantly reduced in the **stimulation** group. In the stimulation group, 16 patients (47%) were completely dry and ten patients (29%) showed a greater than 50% reduction in incontinence episodes. In the **delay** group (controls), the average incontinence episodes increased during six months of conservative therapy from 2.6 +/- 3.5 heavy episodes a day at baseline to 3.9 +/- 3.8 heavy episodes a day at six months. After 18 months, the efficacy appeared to be sustained. During the therapy evaluation at six months, the **stimulation** group returned to baseline symptoms when stimulation was stopped.

Table 3 Different groups have published their longterm results in recent years. They all conclude that SNS therapy is safe and effective[24]

challenges. The sacral dermatomes may be used as an alternative stimulation site.[25] In principle, detrusor inhibition is only needed in case of an involuntary detrusor contraction and electrical stimulation can thus be initiated when intravesical pressure starts to rise and stopped when the pressure has returned to baseline.[25] This technique is called conditional or event-driven stimulation. Conditional stimulation has been shown to be as least as effective as continuous stimulation and may reduce habituation of the involved reflex arches.[25]

Several studies have shown beneficial effects from stimulating the sacral dermatomes in DO. The studies showed there was a minimal effect on urodynamic data, but irritative urinary symptoms, 24-hour urinary frequency, incontinence and 'clothes changing' improved significantly.[25] Suppression of detrusor contractions may possibly only be obtained with stimulation of the dermatomes in the perianal region involving activation of pudendal afferents. Unfortunately, this stimulation site is not attractive for chronic stimulation since sitting on the electrodes and wires may cause skin problems.[26]

DPN stimulation increased bladder capacity and reduced the number of incontinence episodes in ten of the 12 patients by inhibiting the preganglionic bladder motor neurons.[26] Since transcutaneous stimulation of the sacral dermatomes was unable to suppress detrusor contraction, DPN stimulation is left as the best option for a surface-electrode-based conditional system.[25] To avoid surface electrodes in the genital region another approach to stimulate the posterior tibial nerve, also known to inhibit detrusor contractions, may be used. The acute effects of posterior tibial nerve stimulation, however, have not yet been reported in literature.[25]

From this preliminary data, an important issue is to find the best parameters of stimulation and duration of application of the therapy. Further studies must be carried out to identify the best selection criteria and to verify the longterm results.[26]

CONCLUSION

There are many medical and surgical treatments available for neurogenic urinary incontinence. However, each patient needs to be assessed individually and managed accordingly due to the complexity of their condition(s).

REFERENCES

1 Guys JM, Breaud J, Hery G, Camerlo A, Le Hors H, de Lagausie P. Endoscopic injection with poly-dimethylsiloxane for the treatment of pediatric urinary incontinence in the neurogenic bladder: long-term results. J Urol 2006;175:1106-10

2 Bergman J, Lerman SE, Kristo B, Chen A, Boechat MI, Churchill BM. Outcomes of bladder neck closure for intractable urinary incontinence in patients with neurogenic bladders. J Pediatr Urol 2006;2:528-33

3 Sahai A, Khan M, Fowler CJ, Dasgupta P. Botulinum toxin for the treatment of lower urinary tract symptoms: a review. Neurourol Urodyn 2005;24:2-12

4 Roberts MM. Neurophysiology in neurourolgy. Muscle Nerve 2008;38:815-36

5 Verpoorten C, Buyse GM. The neurogenic bladder: medical treatment. Pediatr Nephrol 2008;23:717-25

6 Fader M, Craggs M. Continence problems and neurological disability. IN: Getliffe K, Dolman M, Thomas S. Eds. Promoting continence: a clinical and research resource. London: Elsevier Science; 2003: Pp338-39

7 Dong D, Xu Z, Shi B, Chen J, Jiang J, Wang H. Urodynamic study in the neurogenic bladder dysfunction caused by intervertebral disk hernia. Neurourol Urodyn 2006;25:446-50

8 Kumar A, Chadda RK, Kumar N, Balan S, Srinivasan SP. Clozapine for the treatment of neurogenic bladder. Neurourol Urodyn 2007;26:537-39

9 Karsenty G, Denys P, Amarenco G, *et al*. Botulinum toxin A (BotoxW) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Eur Urol 2008;53:275-87

10 Reddy PR, Borgstein NG, Nijman RJM, Ellsworth PI. Long-term efficacy and safety of tolterodine in children with neurogenic detrusor overactivity. J Pediatr Urol 2008;4(6):428-33

11 Denys P, Schnitzler A, Roche N. Managing patients with neurogenic detrusor overactivity – a global approach. Eur Urol Suppl 2006;5:691–95

12 Feifer A, Corcos J. Contemporary role of suprapubic cystostomy in treatment of neuropathic bladder dysfunction in spinal cord injured patients. Neurourol Urodyn 2008;27:475-79

13 Guerra LA, Moher D, Sampson M, Barrowman N, Pike J, Leonard M. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. J Urol 2008;180:1091-97

14 Giannantoni A, Mearini E, Del Zingaro M, Porena M. Six-year follow-up of botulinum toxin A intradetrusorial injections in patients with refractory neurogenic detrusor overactivity: clinical and urodynamic results. Eur Urol 2008. (2 September, Epub ahead of print)

15 Mascarenhas F, Cocuzza M, Gomes CM, Lea N. Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. Neurourol Urodyn 2008:27:311-14

16 Schulte-Baukloh H, Schobert J, Stolze T, Sturzebecher B, Wei C, Knispel HH. Efficacy of botulinum-A toxin bladder injections for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients: an objective and subjective analysis. Neurourol Urodyn 2006;25:110-15

17 Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC. Botulinum A toxin injections into the detrusor: an e¡ective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005;24:231-36

18 Comperat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity – a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. Eur Urol 2006;50:1058-64

19 Gonzalez R , Myers S, Franc-Guimond J, Piaggio L. Surgical treatment of neuropathic urinary incontinence in 2005. When, what, and how? J Pediatr Urol 2005;1:378-82

20 Snodgrass WT, Elmore J, Adams R. Bladder neck sling and appendicovesicostomy without augmentation for neurogenic incontinence in children. J Urol 2007;177:1510-15

21 Stoffel JT, McGuire EJ. Outcome of urethral closure in patients with neurologic impairment and complete urethral destruction. Neurourol Urodyn 2006:25:19-22

22 Tan H, Stoffel J, Daignault S, McGuire EJ, Latini JM. Ileovesicostomy for adults with neurogenic bladders: complications and potential risk factors for adverse outcomes. Neurourol Urodyn 2008;27:238-43

23 Fiori M, Gunelli R, Mercuriali M, Bercovich E. Tension-free vaginal tape and female stress incontinence: further evidence of effectiveness. Urol Int 2004;72:325-28

24 Oerlemans DJAJ, van Kerrebroeck PEV. Sacral nerve stimulation for neuromodulation of the lower urinary tract. Neurourol Urodyn 2008;27:28-33

25 Fjorback MV, van Rey FS, Rijkhoff NJM, Nohr M, Petersen T, Heesakkers JP. Electrical stimulation of sacral dermatomes in multiple sclerosis patients with neurogenic detrusor overactivity. Neurourol Urodyn 2007;26:525-30

26 Spinelli M, Malaguti S, Giardiello G, Lazzeri M, Tarantola J, van den Hombergh U. A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. Neurourol Urodyn 2005;24:305-9