Neuro-urology for the Urogynaecologist and Urologist

W42, 30 August 2011 14:00 - 18:00

Start	End	Topic	Speakers
14:00	14:05	Introduction to the Workshop	• Sohier Suzy Elneil
14:05	14:25	Neurology of the bladder and the pelvic floor	• Thomas Kessler
14:25	14:45	Bladder Symptoms in the Neurological Patient	• Xavier Game
14:45	15:05	Pelvic Floor Dysfunction in the Neurological Patient	• Alex Digesu
15:05	15:20	Bladder and Pelvic Floor Assement in Neurogenic Bladder and Pelvic Floor Dysfunction	• Xavier Game
15:20	15:30	Discussion	All
15:30	16:00	Break	None
16:00	16:25	Indications and Limitations of Botulinum Toxin in Neurogenic Bladder	• Rizwan Hamid
16:25	16:50	Indications and Limitations of Botulinum toxin in the Pelvic Floor	• Sohier Suzy Elneil
16:50	17:10	Discussion	All
17:10	17:25	Indications and Limitations of Neuromodulation (PTNS) in Neurogenic Bladder and Pelvic Floor Disorders	• Alex Digesu
17:25	17:45	Indications and Limitations of Neuromodulation (SNM) in Neurogenic Bladder and Pelvic Floor Disorders	• Sohier Suzy Elneil • Thomas Kessler
17:45	18:00	Discussion	All

Aims of course/workshop

Aims and Objectives:
-Current concepts relating to the neurogical control of the bladder and the pelvic floor.

-Urinary and pelvic floor symptoms in patients with cerebral leisons, multiple sclerosis, Parkinson's disease, spinal cord injury and cauda equina

-Urinary and pelvic floor symptoms in bladder pain syndrome/IC and chronic pelvic pain syndromes (neurological basis of disease).

-Investigating neurogenic bladder and pelvic floor dysfunction

-Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of botulinum toxin

-Innovative therapies in treating neurogenic bladder and pelvic floor disorders:Indications and limitations of neuromodulation

Educational Objectives

This workshop will provide a fresh approach to the understanding of the neurological basis of bladder and pelvic floor conditions encountered in urogynaecology and urology.

All the speakers have worked extensively in this field and have published widely on the subject matter. Some knowledge of the neurological causes of bladder and pelvic floor dysfunction is essential for the general urogynaecologist and urologist. Patients with neurological disease are referred to both sets of clinicians for advice regarding their bladder and pelvic floor management. It is important to have an understanding of the nature of their neurology, especially when planning medical or surgical management. In addition, clinicians need to know what may be the presenting uro-genital symptoms of a patient with a neurological condition, and the minimal neurological examination necessary for recognising an underlying neurological problem.

The areas covered in this workshop will help clinicians understand the neurological patient with bladder and pelvic floor dysfunction better. The speakers will discuss patient assessment, investigations and provide algorithms for managing this group of complex patients.

NEURO-UROLOGY FOR THE UROGYNAECOLOGIST AND UROLOGIST

Chairman: Sohier Elneil

Introduction

The pelvic floor is highly complex structure made up of skeletal and striated muscle, support and suspensory ligaments, fascial coverings and an intricate neural network. Its dual role is to provide support for the pelvic viscera (bladder, bowel and uterus) and maintain functional integrity of these organs. In order to maintain good pelvic floor function, this elaborate system must work in a highly integrated manner. When this is system if damaged, either directly or as a consequence of an underlying neurological condition, pelvic floor failure ensues along with organ dysfunction.

The aetiology is inevitably multi-factorial, and seldom as a consequence of a single aetiological factor. It can affect one or all three compartments of the pelvic floor, often resulting in prolapse and functional disturbance of the bladder (urinary incontinence and voiding dysfunction), rectum (faecal incontinence), vagina and/or uterus (sexual dysfunction). This compartmentalisation of the pelvic floor has resulted in the partitioning of patients into urology, gynaecology, colo-rectal surgery or neurology, depending on the patients presenting symptoms. In complete pelvic floor failure, all three compartments are inevitably damaged resulting in apical prolapse, with associated organ dysfunction. It is clear that in this state, the patient needs the clinical input of at least two of the three pelvic floor clinical specialities. Whilst the primary clinical aim is to correct the anatomy, it must also be to preserve or restore pelvic floor function. As a consequence, these patients need careful clinical assessment, appropriate investigations, and counselling before embarking on a well-defined management pathway. The latter includes behavioural and lifestyle changes, conservative treatments, pharmacotherapy, minimally invasive surgery, and radical specialised surgery.

It is not surprising that in this complex group of patients, a multidisciplinary approach is not only necessary, but critical, if good clinical care and governance is to be ensured. But it is of significant import that one has a good understanding of the neurology of the pelvis and its organs.

Neural control of uro-genital system

Voluntary control over the uro-genital system is critical to our social existence. Since its peripheral innervation derives from the most distal segments of the spinal cord, integrity of

the long tracts of the central nervous system for physiological function is immediately apparent. In a survey of the site of the underlying neurological disease affecting a sample of patients referred to the department with bladder symptoms, spinal cord involvement of various pathologies was found to be the commonest cause of bladder symptoms.
Because of the commonality of innervation shared by the bladder and genital organs, it might be expected that abnormalities of these two systems inevitably occur together. This however is not the case because although the organs share the same root innervation and have common peripheral nerves within the pelvis, each is controlled by its own unique set of central nervous system reflexes.

In this workshop, a brief account of the neurophysiological control of the bladder and pelvic is given initially, followed by a description of the effect that neurological disease at different levels of the nervous system may have and finally the management of those conditions.

The bladder performs only two functions - storage and voiding of urine- and the modern view of the control of these two mutually exclusive activities is that whereas storage is organised within the spinal cord, micturition results from activation by suprapontine influences of a centre in the dorsal tegmentum of the pons, the pontine micturition centre (PMC). In neurological disease, this delicate interaction can be severely disrupted, and manifests as a disorder of voiding or storage depending on the condition such as multiple sclerosis, Parkinson's disease, multiple system atrophy and others. But commonly, it is direct injury to pelvic nerves that can give rise to quite marked bladder and pelvic floor dysfunction.

The peripheral innervation of the pelvic organs can be damaged by extirpative pelvic surgery such as resection of rectal carcinoma, radical prostatectomy, or radical hysterectomy. The dissection necessary for rectal cancer is likely to damage the parasympathetic innervation to the bladder and genitalia, as the pelvic nerves take a medio-lateral course through the pelvis either side of the rectum and the apex of the prostate. The nerves may either be removed together with the fascia which covers the lower rectum or may be damaged by a traction injury as the rectum is mobilized prior to excision.

Urinary incontinence following a radical prostatectomy or a radical hysterectomy which includes the upper part of the vagina, is probably also due to damage to the parasympathetic innervation of the detrusor and in the case of a radical prostatectomy, there may be additional direct damage to the innervation of the striated urethral sphincter

The focus in the literature tends to focus on the effects of neurological disease on the bladder tends, but other pelvic floor effects should not be ignored, such as pelvic organ prolapse, pain syndromes and sexual dysfunction.

Therapies to manage these conditions depend on a multi-disciplinary approach. This workshop will help guide practitioners on how to maximise the therapeutic options for their patients.

Aims and Objectives of the Workshop

- Current concepts relating to the neurological control of the bladder and the pelvic floor.
- Urinary and pelvic floor symptoms in patients with cerebral lesions, multiple sclerosis, Parkinson's disease, spinal cord injury and cauda equine
- Urinary and pelvic floor symptoms in bladder pain syndrome/IC and chronic pelvic pain syndromes (neurological basis of disease).
- Investigating neurogenic bladder and pelvic floor dysfunction
- Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of botulinum toxin
- Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of neuromodulation

Neurology of the bladder and the pelvic floor (Assistant Professor Thomas Kessler)

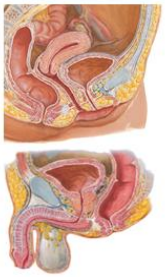
Please insert document by Assistant Professor Thomas Kessler

Bladder and Pelvic Floor Symptoms in the Neurological Patient (Dr Xavier Game)

Neurological dysfunction of the bladder

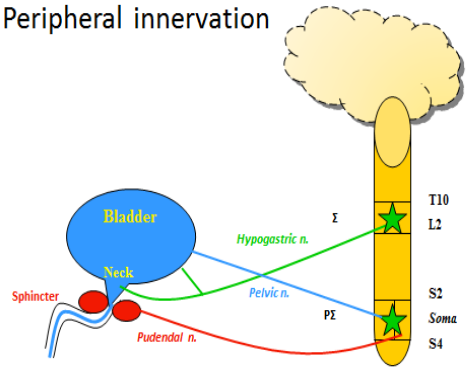
Xavier Gamé
Dept of Urology, Kidney Transplantation and Andrology
University Hospital Rangueil
Toulouse-France

Bladder : Anatomy and function

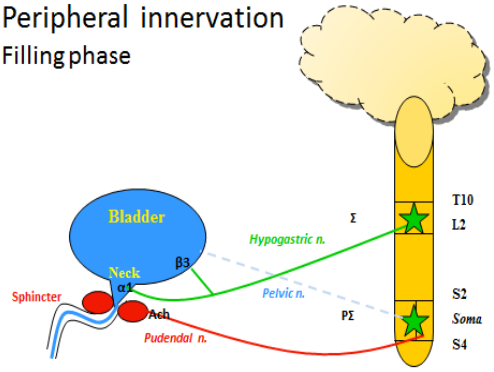


- Urinary storage : 99 %
- Passing urine : 1 %

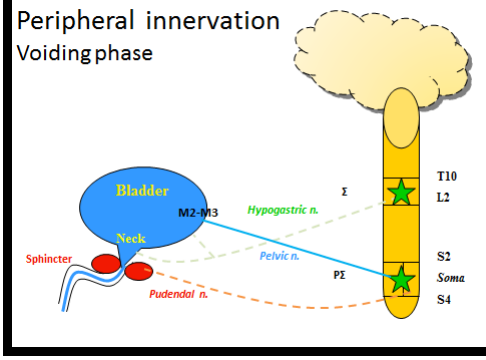
Peripheral innervation



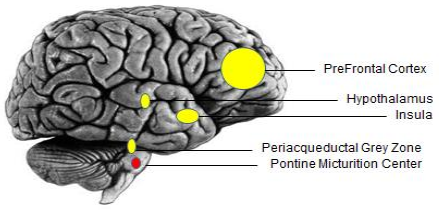
Peripheral innervation
Filling phase



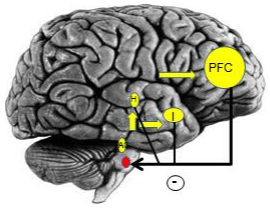
Peripheral innervation
Voiding phase



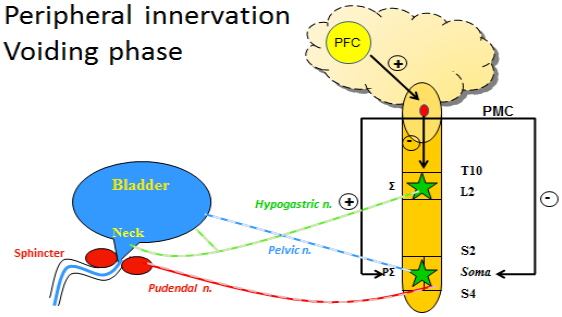
Under Brain control



Under Brain control
Filling Phase

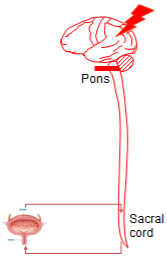


Peripheral innervation
Voiding phase



Neurological conditions

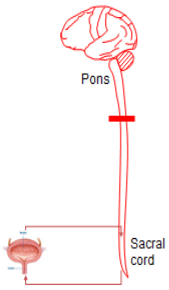
Suprapontine lesions



- Overactive bladder syndrome
- Intact neural programs → synergy between detrusor and sphincter

- Parkinson disease
- Stroke
- Multiple sclerosis

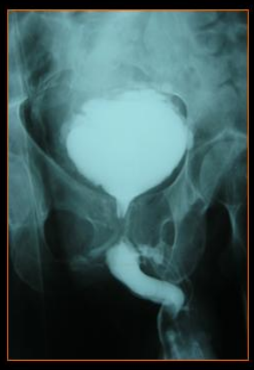
Spinal cord lesion
(Above T10)



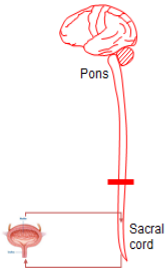
- Automatic bladder
- Reflex bladder

- Overactive bladder
- Detrusor Sphincter Dyssynergia

- SCI patients
- Multiple sclerosis
- Myelitis ...

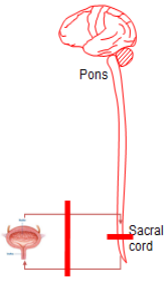


Lower cord lesion
(below T10)



- Intact sympathetic innervation to internal sphincter
- Variable integrity of neural programs: less dyssynergia
  → Hesitancy, low stream, incomplete voiding

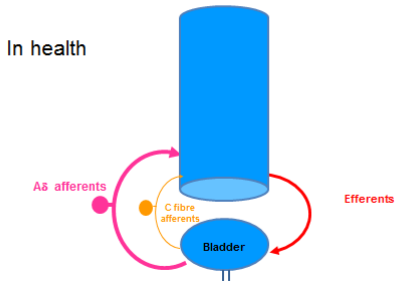
Autonomous bladder

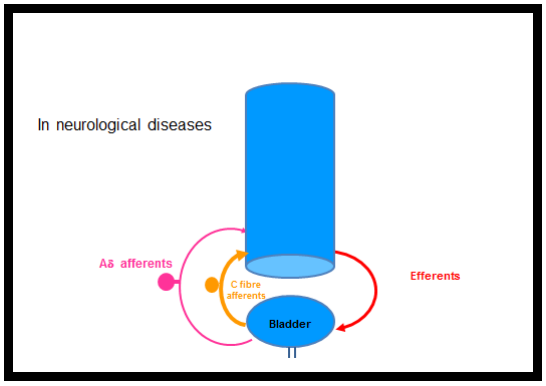


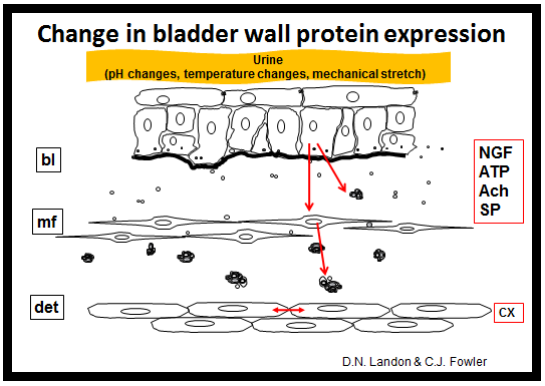
- Lesion of conus or cauda equina
- No voluntary or reflex control
- Tumours, spina bifida, necrotizing myelitis, trauma, cauda equina syndrome, neuropathy

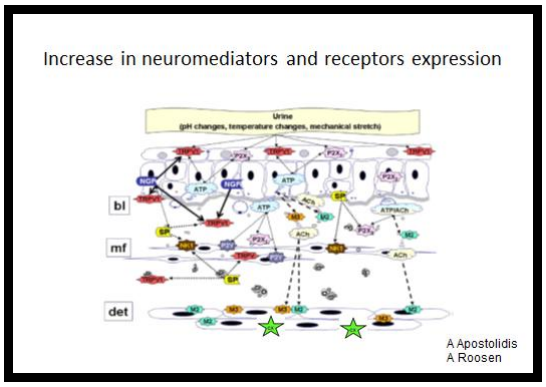
And the bladder wall

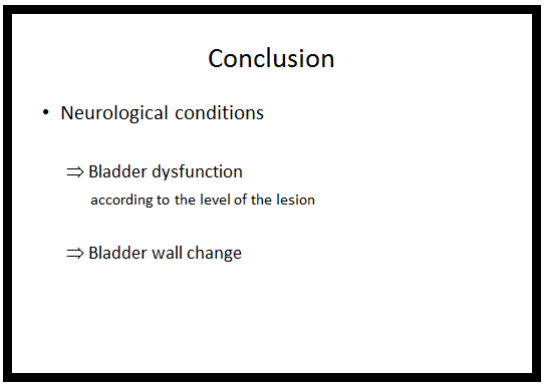
Change in nerve fibers distribution











Neurogenic Basis of Bladder Pain Syndrome and Interstitial Cystitis (Sohier Elneil)

Bladder pain syndrome (BPS) is a debilitating chronic disease characterized by bladder pain that increases with bladder filling, and is accompanied by symptoms of increased daytime and night time frequency and urgency in the absence of proven urinary infection or other obvious underlying condition [1]. The extreme of these complex symptoms of bladder dysfunction is interstitial cystitis (IC). Epidemiological surveys in USA report that between 700,000 and 1,000,000 people, mainly women, are suffering from the condition, with an estimated prevalence between 30 and 67 per 100,000 population [2] [3]. It is known to have a detrimental impact on patients' quality of life. No data exist so far on the frequency of interstitial cystitis in the United Kingdom, and large-scale studies in Finland and the Netherlands have reported a much lower frequency than in the USA with prevalence rates of 18.1 and 16 per 100,000 population [4] [5]. A questionnaire-based survey of the Interstitial Cystitis Support Group in the UK recorded frequency in 92% of patients, nocturia in 87%, urgency in 84%, bladder pain in 63% and urethral pain in 63%. Forty-seven per cent of

participants reported suffering from moderate to severe depression and in 67.3% the impact of LUTS on everyday life was considerable [6].

The aetiology of BPS/IC remains unknown. A variety of factors have been implicated, including inflammation, autoimmune disorders, allergy, viral and/or bacterial subclinical infections, neurogenic inflammation, and urothelial dysfunction.

Increased urothelial permeability has been strongly implicated in the pathophysiology of IC. A significantly lower proliferation rate of urothelial cells was found in bladders of IC patients compared to control bladders [7]; an antiproliferative factor (APF) made by urothelial cells was detected in the urine of IC patients [8]. In a multivariable analysis of the predictive power of histopathology features for urinary symptoms in IC, denudation of the bladder mucosa from urothelium was significantly associated with pain and nocturia [9]. In relevance, bladder pain upon instillation of KCl is thought to be indicative of a permeable urothelium, through which K^+ leak depolarises bladder afferents; a positive KCL test has been suggested amongst the diagnostic criteria for IC [10]. Afferent neuromodulation through an abnormally permeable urothelium has been proposed as the possible mechanism by which high concentrations of intravesical KCL could almost abolish afferent neural activity in cats with feline IC [11]. Finally, inducible nitric oxide synthase (iNOS) and nitric oxide (NO) levels were significantly increased in feline IC bladders [12]. Luminal NO production was found to be decreased only in IC patients that responded to treatment, and changes in NO levels correlated well with changes in symptom/bother score [13].

There is increasing evidence for a role of abnormal afferent activity in the pathophysiology of IC, via increased expression of sensory receptors and/or release of neuropeptides and neurotransmitters associated with the sensation of bladder fullness and perception of visceral pain. Bladder afferents in cats with feline IC showed increased firing in response to various levels of intravesical pressure compared to normal cats, suggesting increased mechanoreceptor sensitivity in this condition [11]. Stretch-evoked ATP release from urothelial cells is increased in patients with IC compared to controls [14]. In addition, $P2X_3$ expression was upregulated in the urothelium of IC patients [15] and stretch of cultured urothelial cells from IC bladders resulted in higher $P2X_3$ expression compared to stretch of ‘normal’ cells [16]. Increased numbers of SP-immunoreactive fibres have been found in the suburothelium of IC patients in comparison to controls [17], while SP receptor-encoding mRNA was found to be increased within the vascular endothelium of IC bladders [18].

Women with IC have increased mean urine concentration of SP compared to age-matched controls, which correlated significantly with urinary frequency and urgency in those treated with dimethylsulfoxide (DMSO) [19]. Also, decrease in urine SP levels after epidural anaesthesia was accompanied by successful pain control in IC patients [20]. In support of neuroplastic changes in IC bladders, NGF immunoassay levels were found to be increased in such bladders, with increased NGF immunoreactivity localising in the bladder urothelium, but not in the muscular component of the biopsies [21]. Furthermore, significant attenuation of pain and urgency in IC patients treated with intravesical instillation of alkalinised lidocaine, which is known to have an inhibitory effect on neurite regeneration and synapse formation [22], suggested modulation of bladder afferents and provided further evidence for a role of the afferents in the pathophysiology of IC [23].

The condition is also characterised by the presence of long-standing inflammation in the bladder. Bladder mastocytosis and increased activation of mast cells have been associated with the pathophysiology of IC, and increased urinary levels of mast cell mediators have been found in these patients [24]. Mast cells are often in close apposition to nerve fibres and can be activated by SP and carbachol [25], suggesting a neuro-immunomodulatory role. Activation of bladder mast cells can be potentiated by estradiol [25]. Bladder mast cells were shown to express high-affinity oestrogen receptors and a higher number of such cells were present in patients with IC compared with controls [26].

Treatment of BPS

Despite the use of several oral and local agents, no effective treatment has been found to date. A questionnaire-based survey in the UK showed that antidepressants, antibiotics, anti-inflammatory drugs, antihistamines, anticholinergics, anticonvulsants, cimetidine, sodium citrate, sodium bicarbonate, DMSO and pentosan polysulphate are commonly used non-invasive treatments in this country, while 4.9% of patients asked had undergone urinary diversion or cystoplasty [6]. Intravesical instillation of a solution combining heparin and alkalinised lidocaine provided immediate relief of pain in 75% (lidocaine 1%) and 94% (lidocaine 2%) of patients treated, but this can only last for 2 weeks with repeat treatment. Based on findings suggesting an anti-nociceptive effect of BoNT/A through modulation of sensory pathways that may also be involved in the pathophysiology of BPS/IC, it was thought highly likely that patients with BPS/IC would benefit from bladder injections of BoNT/A and a single study to date has examined the effect of BoNT/A on IC; Smith et al injected suburothelially up to 200 units Botox® or equivalent Dysport® in 13 patients, and reported significant improvements in symptom scores in 9 (70%) of them [27]. Frequency,

nocturia, maximum cystometric capacity and cystometric volume at first desire to void improved significantly, while pain decreased by a mean 79%. No systemic side effects or cases of urinary retention were reported, and symptomatic improvement lasted for a mean 3.7 (range 1-8) months.

Role of Botulinum Toxin A

The mechanism of action of Botulinum neurotoxin type A (BoNT/A) has been extensively investigated in striated muscle, where it is known to act by prolonged selective blockade of acetylcholine (ACh) exocytosis after its intracellular proteolytic cleavage of the synaptosome-associated protein SNAP-25. Recovery of neurotransmission occurs eventually as functional axonal sprouts emerge from the spared nerve terminals. These then regress gradually, whilst the original terminals recover their function [28] [29] [30] [31] [32] [33] [34].

Over the past 9 years, the use of BoNT/A (Botox®, Dysport®) has been pioneered in the treatment of lower urinary tract symptoms (LUTS) such as urgency, frequency and urgency incontinence due to intractable neurogenic (NDO) or idiopathic (IDO) overactivity of the detrusor smooth muscle of the bladder. BoNT/A injected into the bladder wall of such patients has produced exceptional improvements in both LUTS and urodynamic parameters, with response rates approaching 95-100% in some reports [35] [36]. The duration of clinical improvement is 6-11 months [37] [38] and repeat treatments appear to have sustained effects [38]. In an on-going study we have so far used intradetrusor injections of Botox® in 100 patients, 63 with NDO and 37 with IDO. Of those with available follow-up data, all but one have responded to the treatment, group analysis showing significant improvements in mean maximum cystometric capacity, maximum detrusor pressure during filling cystometry, 24-hour frequency, number of incontinence episodes per 24 hours and number of voids associated with urgency per 24 hours [36]. Symptomatic improvement is an early feature of the patients' clinical response occurring within the first week [39]. Amelioration of symptoms is accompanied by significant improvement in patients' quality of life [39] [40].

Intradetrusor BoNT/A, however, remains an unlicensed treatment and its mode of action in the human bladder is largely unknown. Although clinical and urodynamic results suggest a long-lasting, but reversible 'paralysis' of the detrusor due to parasympathetic motor deficiency similar to the mechanism of action in striated muscle, biopsies from the detrusor of treated NDO patients showed no significant ultrastructural nerve changes (degeneration or sprouting) [41]. Furthermore, an immunohistochemical study of flexible cystoscopic biopsies from patients treated in our department showed that suburothelial nerve density measured by immunoreactivity to the pan-neuronal marker PGP9.5 (protein gene product

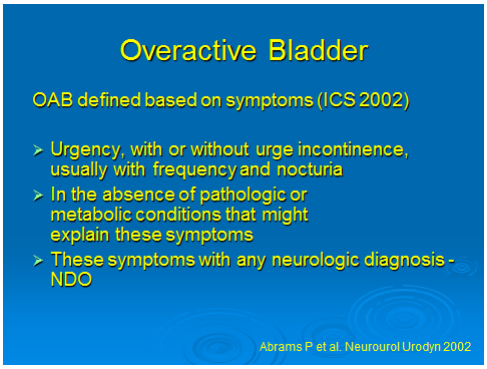
9.5) remained unchanged after treatment. In the same biopsies, a significant post-BoNT/A decrease in the levels of the capsaicin receptor TRPV1 and the purinergic receptor $P2X_3$ in suburothelial nerves suggested an effect of BoNT/A on bladder afferent pathways [42]. Both receptors have been shown to be involved in normal bladder mechano-sensation in animal studies; TRPV1-knockout mice display changes in voluntary micturition pattern as well as increased frequency of non-voiding contractions on urodynamics, increased cystometric capacity and inefficient voiding [43]. $P2X_3$-deficient mice exhibit increased cystometric capacity and decreased frequency of voiding [44] [45]. TRPV1 activation is required for distension-evoked release of ATP and NO from the urothelium [43]; urothelially-released ATP is believed to act as a sensory mediator for the degree of bladder distension, via its action at suburothelial $P2X_3$-receptors [46] [47]. Of relevance here, BoNT/A significantly inhibited the distension-evoked release of ATP from the bladder urothelium in rats with chronic spinal cord injury [48].

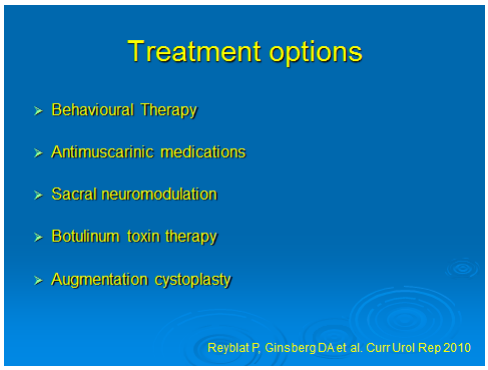
The presence of TRPV1 and NOS has been also shown in the recently described human bladder interstitial cells [49], which are extensively linked by connexin 43-containing gap junctions in the suburothelium [50]. These cells bear several morphological characteristics of the myofibroblasts that have been recently identified in the human bladder suburothelium, lying in close proximity to vesicle-packed unmyelinated nerve endings [51]. It was proposed that the myofibroblasts/interstitial cells and their closely associated axonal varicosities could collectively function as a bladder stretch receptor. Electrophysiological experiments have shown that guinea pig suburothelial 'myofibroblasts' may respond to ATP by an increase in intracellular Ca^{2+} and generation of an inward current in a manner similar to the activation of ATP-gated P2Y receptors [52], whereas substance P (SP) activated high affinity receptors in interstitial cells in the guinea pig small intestine [53].

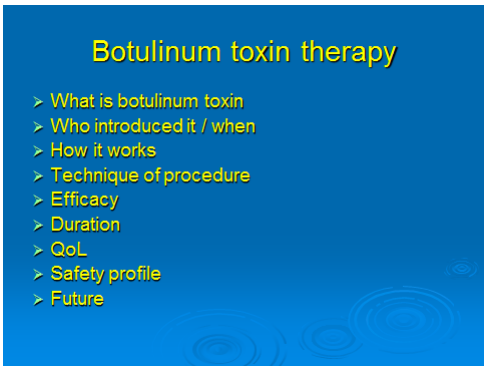
Importantly though, both TRPV1 and $P2X_3$ are also known to be involved in pain pathways, and TRPV1- and $P2X_3$-deficient mice demonstrated impaired nociception [54] [44]. A peripheral anti-nociceptive effect of BoNT/A has been demonstrated in animal models of formalin-induced inflammatory pain via inhibition of the release of the neurotransmitter glutamate. BoNT/A was shown to specifically affect the second phase of neurogenic inflammation, which is known to be mediated by the sensory neuropeptides SP and calcitonin gene related peptide (CGRP) [55]. An effect of BoNT/A on the release of SP was found in cultured dorsal root ganglion (DRG) cells following cleavage of SNAP-25 [56], while intravesical instillation of BoNT/A in a rat model of bladder inflammation resulted in inhibition of mucosal release of CGRP and afferently mediated bladder overactivity [57]. Further evidence for modulation of nociceptive afferent pathways by BoNT/A was provided when a BoNT/A-conjugate was shown to induce inhibition of SNARE-dependent, presumably

vesicular, release of SP and glutamate from rat DRG cells with significant attenuation of the sensory transmission from C-fibre afferents through the spinal cord [58]. A dose-dependent reduction in the expression of Fos in the dorsal horn of the formalin-challenged rat model [55] suggested that the initial peripheral desensitization induced by BoNT/A is followed by a central one, through reduced nociceptive input to the spinal cord [59].

Indications and Limitations of Botulinum Toxin in Neurogenic Bladder and Pelvic Floor Disorders (Rizwan Hamid)







The development of BOTOX® for therapeutic use

2010	BOTOX® injection therapy is the only product specifically licensed for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
2002	BOTOX® received UK approval for treatment of initial and hand disability due to upper limb spasticity associated with stroke in adults
2001	BOTOX® approved for the treatment of axillary hyperhidrosis (excessive sweating) in the UK
1998	BOTOX® received UK approval for dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients aged 2 years and older
1997	BOTOX® approved for the treatment of the symptomatic relief of idiopathic cervical dystonia in the UK
1994	BOTOX® approved in the UK for the treatment of hemifacial spasm (a neuromuscular disorder characterised by unpredictable and involuntary twitching of the facial muscles on one side of the face) and blepharospasm
1989	Allergan, Inc., receives approval from the Food & Drug Administration (FDA) for the name BOTOX® (botulinum toxin type A, Oculinum) and gets FDA approval to market BOTOX® for strabismus and blepharospasm (uncontrollable eye blinking) associated with dystonia
1988	Allergan requires rights to distribute Dr Scott's botulinum toxin type A, Oculinum
1980s-70s	Purification process of botulinum toxin type A optimised. Alan. B. Scott, M.D., Smith Kettlewell Eye Research Foundation, San Francisco, tests efficacy of toxin as treatment for crossed eyes (strabismus). Dr Scott forms company, Oculinum Inc. to conduct human testing
1960s	Dr Vernon Brooks proves botulinum toxin blocks acetylcholine release from motor neuron endings, inducing a temporary 'relaxation' of the targeted muscle
1946	Botulinum toxin type A isolated in crystalline form by Edward J. Schantz, Ph.D., University of Wisconsin-Madison
1920s	Botulinum toxin type A isolated in purified form by Doctor H. Sommer, University of California, San Francisco, USA
1896	Bacterium Bacillus botulinum (later renamed Clostridium botulinum) identified by Prof E. P. van Ermengem, a bacteriology professor at the University of Ghent, Belgium

Botulinum Toxin A

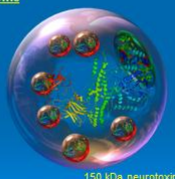
Mechanism of action

- Seven subtypes (A,B,C1,D,E,F,G)
- Clinically A & B used. (A more potent)
- Enters pre-synaptic endplate of cholinergic neurons by receptor mediated endocytosis.
- Selectively cleaves SNAP-25- prevents normal vesicle docking & fusion to the presynaptic plasma membrane
- Inhibits the release of neurotransmitters (no effect on production and storage of transmitters)
- It reduces the level of sensory receptors (TRPV1 & P2X3) in suburothelium. Hence decreased sensitivity of the aberrant unmyelinated C fibres
- BTX cannot cross the blood-brain barrier
- Doesn't- alter detrusor structure, induce muscle cell degeneration,induce axonal sprouting

Botulinum Toxin: *Unique Molecular Structure*

Clostridium botulinum is a gram positive, anaerobic, rod-shaped bacterium that produces seven serologically distinct neurotoxins (A, B, C1, D, E, F, G)

Non-Toxic Accessory Proteins



Non-toxic, non-hemaglutinin (NTNH)

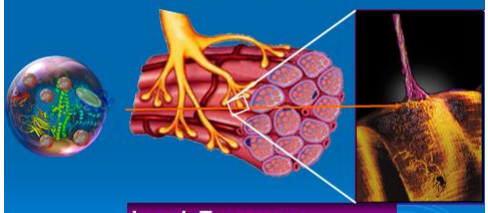
Hemaglutinin (HA)

150 kDa neurotoxin protein

Modular Design Imparts Activity

Schantz EJ Gasper E (1975) Jpn J Med Sci Biol 28:56-69

BTX has high affinity for the Neuromuscular Jn



Local, Temporary, Muscle Relaxation

Botulinum Toxin Type A Mechanism: *alpha* Motor Neuron Inhibition

- BTX-A binds to acceptors on cholinergic terminals
- Internalization

- Release of light chain
- Cleavage of SNAP-25 and blockage of ACH release

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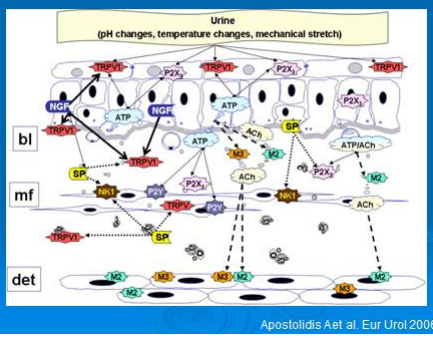
Review - Neuro-urology – Voiding Dysfunction

Proposed Mechanism for the Efficacy of Injected Botulinum Toxin in the Treatment of Human Detrusor Overactivity

Apostolos Apostolidis [a], Prokar Dasgupta [a,b], Clare J. Fowler [a,*]

[a] Department of Uro-Neurology, the National Hospital for Neurology and Neurosurgery, London, UK
[b] Department of Urology, Guys' and St. Thomas' Hospitals and GKT Medical School, London, UK



Apostolidis A et al. Eur Urol 2006

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Vol. 164, 692–697, September 2000
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BOTULINUM-A TOXIN FOR TREATING DETRUSOR HYPERREFLEXIA IN SPINAL CORD INJURED PATIENTS: A NEW ALTERNATIVE TO ANTICHOLINERGIC DRUGS? PRELIMINARY RESULTS

B. SCHURCH,* M. STÖHRER, G. KRAMER, D. M. SCHMID, G. GAUL AND D. HAURI

From the Swiss Paraplegic Centre, University Hospital Balgrist and Departments of Urology, University Hospital, Zurich and BG Unfallklinik, Murnau, Switzerland

'Penicillin for the 21st century'

Botulinum toxin A

- Popularised by Schurch
- Unlicensed indication
- 2nd line (refractory to medications)
- Temporary (ave 8-9 months)
- Repeated injections are effective
- Need for self catheterization
- Local / GA
- Number / site / dose not well defined

Points of Technique

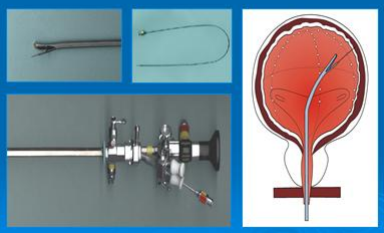
A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity

M. HARPER, R.B. POPAT, R. DASGUPTA, C.J. FOWLER and P. DASGUPTA*

*Department of Uro-Neurology, National Hospital for Neurology and Neurosurgery, and *Department of Urology, Guy's and St Thomas' Hospital, London, UK*

Accepted for publication 31 March 2003

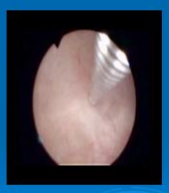
Surgical Procedure



Technique of injection

Via flexible cystoscope

- Dose
  - Botox 200IU
- Site of injections
  - Avoid the trigone
- Number of injections
  - Vary in number, but usually 20



Botox injection technique

Pubmed search

	2000	2002	2004	2006	2008	2010
BTX	1	3	6	35	44	57
Anti-choli	3	15	13	32	24	28
SNS	1	3	3	5	14	19

European Consensus Report

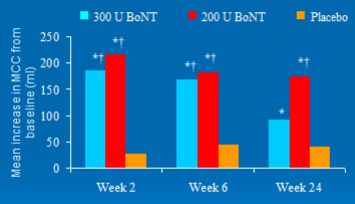
- 200 IU BTX
- Mostly intradetrusor injections
- Efficacy 36-89% (mean 69%)
- Complete continence 32-86% (mean 58%)
- Duration of effect 4-10 mo (mean 6 mo)

- MCC – increased (11-242%)
- Pdet – decreased (9-56%)

- PVR (4-45%)
- UTI's (6-35%)
- Haematuria (3-5%)
- Malaise (5%) / Flu-like symptoms
- Hypothenia
- No fibrosis

Apostolides A et al. Eur Urol 2009

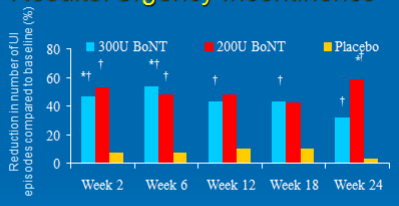
Results: Urodynamics – MCC



*p<0.05 for within-group changes from baseline
†p<0.05 for pairwise contrasts between BoNT groups versus placebo

Schurch. J Urol, 2005

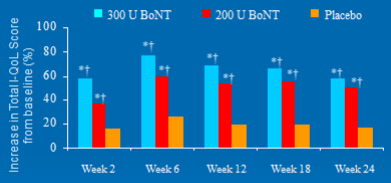
Results: Urgency Incontinence



*p<0.05 for differences between BoNT group and placebo
†p<0.05 for difference within-group changes from baseline

Schurch. J Urol, 2005

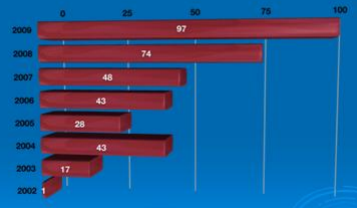
Results: Quality of Life



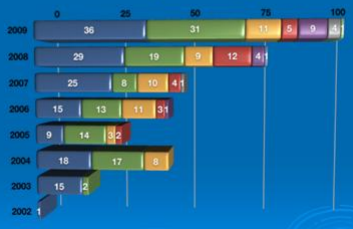
*p<0.05 for pairwise contrasts between BoNT groups and placebo
†p≤0.002 for within-group differences from baseline

Schurch. J Urol, 2005

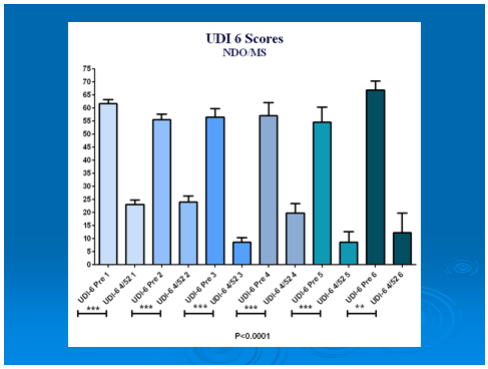
Number of NDO/MS patients treated by BoNT-A

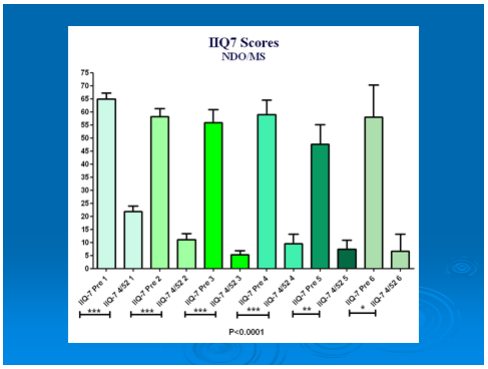


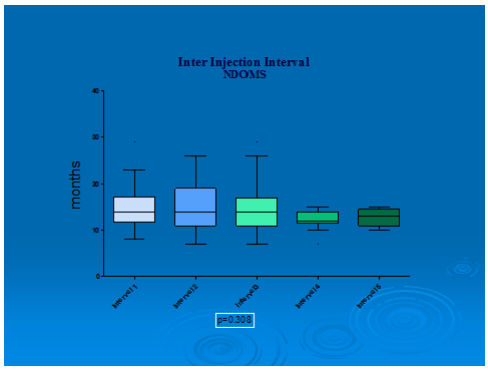
New v/s repeat injections

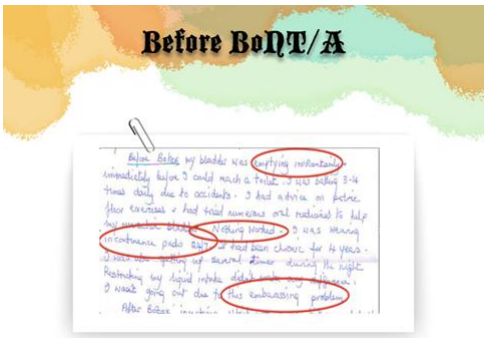


Pain Perception









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European Association of Urology

Neuro-urology

Histological Changes in the Urothelium and Suburothelium of Human Overactive Bladder following Intradetrusor Injections of Botulinum Neurotoxin Type A for the Treatment of Neurogenic or Idiopathic Detrusor Overactivity

Apostolos Apostolidis [a,b], Thomas S. Jacques [c], Alex Freeman [d], Vinay Kalsi [a,b], Roshni Popat [b], Gwendoline Gonzales [b], Soumendra N. Datta [a,b], Shabnam Ghazi-Noori [b], Sohier Elneil [b], Prokar Dasgupta [a,e], Clare J. Fowler [a,b,*]

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[b] Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, UCLH, London, United Kingdom
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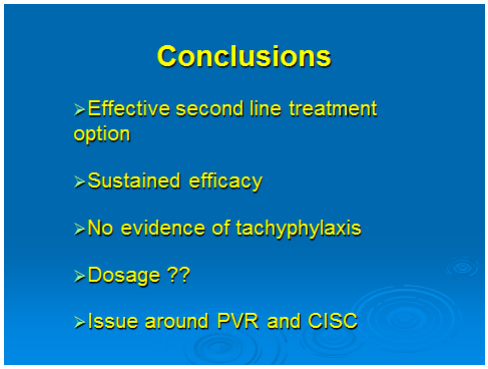
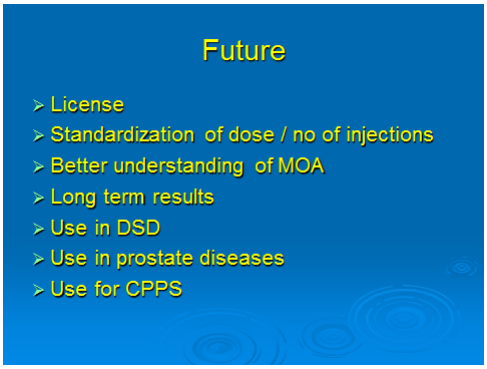
[d] Department of Histopathology, University College Hospital, London, United Kingdom
[e] Department of Urology, Guys' and St Thomas' Hospitals, London, United Kingdom

Conclusion

- No Fibrosis
- No Hyperplasia
- No Dysplasia
- Inflammatory changes after BoNT/A





Indications and Limitations of Neuromodulation in Neurogenic Bladder (Alex Digesu)

The pelvic floor plays an important role in the urine storage, voiding, urine continence, anal continence to gas and feces, defecation and sexual activity. All these pelvic organ functions are controlled by nervous pathways that involve neurons in the motor cortex of the brain, spinal cord and peripheral ganglia.

In neurological diseases the alteration of these nervous pathways are responsible of the lack of coordination between the urinary bladder, urethra, rectum and pelvic floor muscle (PFM) leading to pelvic floor dysfunction (PFD).

Symptoms commonly reported by patients with neurological diseases include urinary incontinence (37–70%), constipation (29–67%), and in men erectile dysfunction (40–60%). This indicates that the central nervous system is involved both in motor and autonomic pelvic functions.

The pathogenesis of PFD in patients with neurological lesions is an active area of research. However, it is still unknown whether PFD are caused by lesions of the central nervous system or peripheral nerves.

It has also been demonstrated that the prevalence of bladder and bowel dysfunction increased with the severity of the illness. Sakakibara et al., showed that the majority of patients with Parkinson's disease experienced pelvic organ dysfunction onset after the appearance of motor disorder.

The most striking feature of bladder dysfunction in the Parkinson's disease patients is filling phase disorder and urinary incontinence. It has been suggested that in those patients, the

decrease in central dopaminergic neurons (D1), which regulate the pontine micturition center, is responsible of detrusor hyperreflexia.

Voiding phase disorder is another feature seen in Parkinson's disease patients due to detrusor-sphincter dyssynergia. This disorder may be caused by peripheral a-adrenergic stimulation by anti-parkinsonian drugs such as levodopa or its metabolites.

However, the effect of dopaminergic drugs on parkinsonian bladder shows conflicting results. In some reports, the use of apomorphine, levodopa, pergolide produced a lessening of detrusor hyperreflexia whereas in others, it provided amelioration of voiding difficulty.

The most common bowel dysfunction in Parkinson's disease patients are constipation and prolonged colorectal transit time, difficulty in expulsion and paradoxical contraction of the puborectal muscle. These symptoms probably, reflect abnormalities in the colon and ano-rectum. Experimental study findings showed that a decreased intestinal motility occurs when there is a reduction in the number of central dopaminergic neurons, which modulate the pontine defecation centre. Other possible causes are peripheral nerve lesions or overextension injury secondary to faecal impaction.

Sexual dysfunction is also very common in both men and women with Parkinson's disease. However, the mechanism of sexual dysfunction is less clear than that of bladder and bowel dysfunction. Whereas motor disorder, pain, and depression may affect sexual function, there is little evidence that autonomic dysfunction contributes to sexual dysfunction in those patients. Experimental studies have shown that the key area for sexual function is in the hypothalamus and particularly the medial preoptic area and paraventricular nucleus.

People with multiple sclerosis experience high levels of sexual dysfunction which are mainly represented by hypoactive sexual behaviour, lack of sexual interest, decreased libido, often with problems in orgasmic capacity. Fatigue, spasticity, muscular weakness, bladder problems, pain, cognitive and behavioural changes also has an important impact on sexual dysfunction.

Different neurophysiological tests have been proposed in order to assess the direct and reflex responses to the pelvic floor. These include: the pudendoanal reflex, the bulbocavernosus reflex, the pudendal nerve terminal motor latency (PNTML). The cutaneoanal reflex and other somatosomatic and viscero-somatic reflexes have limited

usefulness in pelvic floor investigations due to a large variability in the latency of these responses.

The more commonly used electrophysiological investigations to investigate the integrity of the sacral reflex arc supplying pelvic floor muscle function are the PNTML and the sacral reflexes. These last tests can be elicited by mechanical, electrical or magnetic stimulation and involve the whole reflex arc, but do not differentiate the afferent and efferent branch of the reflex.

The PNTML only explores the more distal portion of pudendal nerve, not looking at the portion of the nerve proximal to the site of the stimulation induced by the St. Mark's electrode.

More recently, Fowler et al. described direct and reflex responses after S3 root stimulation, introducing wire electrode close to S3 sacral root. Direct motor and reflex responses from the external anal sphincter (EAS) by S3 electrical stimulation can provide valuable information on the functional integrity of the sacral reflex pathway, but differently from the pudendoanal and bulbocavernosus reflexes, can distinguish the efferent limb of the reflex pathway from the whole arc.

EAS responses during S3 percutaneous electrical stimulation are easy to perform, not invasive neither too painful thus representing a useful electrophysiological technique for the selection of candidates to sacral nerve modulation (SNM). The EAS responses following the stimulation of the same S3 fibres used for SNM, contribute to evaluate the functional integrity of the efferent branch of pudendal nerve and to exclude lesions at the sacral S2-S4 central cord levels.

Peripheral Neuromodulation in Pelvic Floor Disorders (Dr Sohier Elneil)

Electrical neuromodulation of the lower urinary tract began over a century ago, but it was the pioneering work of Tanagho and Schmidt at the University of California in the late 1980s that demonstrated electrical activation of efferent fibres to the striated urethral sphincter inhibited detrusor contractions [60]. Stimulation of the third sacral root (S3) has been shown to be effective in stimulating the urethral sphincter [61]. A large multicentre (Medtronic MDT-103 - USA, Canada and Europe) prospective randomised clinical trial was set up to look at efficacy and safety of chronic neuromodulation to the S3 nerve. Results of this study led to approval by the Food and Drugs Administration in October 1997. Over 25,000 neuromodulators

(Interstim® and Interstim II®, Medtronic Inc, Minnesota, Minneapolis, USA) have so far been implanted for approved urinary indications, including functional non-neurogenic urinary retention or chronic urinary retention and voiding dysfunction secondary to urethral sphincter overactivity (Fowler's syndrome) [62, 63]. . Indeed, SNM has been shown to be the only effective therapy in women with these conditions.

Mechanism of Action in Urinary Retention

Sacral neuromodulation restores voiding in women with chronic urinary retention [64], probably by resetting brainstem function [65]. SNM was first described as a treatment for urinary retention in the mid-1990s. At the time, SNM was introduced for the management of bladder dysfunction, paradoxically both intractable incontinence and retention. The first stage of SNM was an initial test procedure, known as a percutaneous nerve evaluation test (PNE) which if found to be positive and restore voiding ability, was followed by the implantation of a permanent sacral electrode. Success rates for women with retention for this method were reported at 40 – 50% for the PNE, with approximately 60% voiding to completion with formal implantation [66], [67]. In the Department of Uro-neurology at the National Hospital for Neurology and Neurosurgery in London, the author's experience has been comparable, with two thirds of patients continuing to void without need for catheterization at a follow up of 5 years [68].

A retrospective study of 247 women referred to our Department, with urinary retention over a 4-year period showed that Fowler's syndrome is the commonest diagnosis although this only accounts for 58 %. In 32% no diagnosis could be made but in 2% there was a history of chronic opiate ingestion [69]. In 3% of the patients there appeared to be a relationship with chronic idiopathic pseudo-obstruction (CIPO), a rare disorder characterised by severe and chronic constipation without any demonstrable anatomical or mechanical lesion but thought to be due to a visceral neuropathy or myopathy (in infants or children) [70]. In men, there is an uncommon condition where painless urinary retention is present but it is not associated with constipation, and sexual function is preserved, but in whom extensive investigation fails to reveal any underlying abnormality. It has been speculated that this disorder is due to some abnormality of the intrinsic afferent innervation, possibly loss of the "myofibroblast" or interstitial cell, thought to be an integral part of the bladder stretch sensing mechanism [71] although no proof of that exists as yet. Presumably, this same condition makes up a proportion of the women with unexplained urinary retention.

Though the mechanism of action of SNM remains indeterminate, there are various theories based on careful observations. Two components have been identified (i) activation of

efferent fibres to the urethral sphincter with negative feedback to the bladder (pro-continence reflex) and (ii) activation of sacral spinal afferents resulting in inhibitory reflex efferent activity to the bladder. Reflex pathways at the spinal cord and supra spinal levels are thought to be modulated to achieve these effects [72, 73]. The prolonged beneficial effects of the stimulator, after it is switched off, support this observation. In urinary retention, SNM is postulated to interfere with the inhibitory afferent activity arising from the urinary sphincter and thus restoring the sensation of bladder filling and the ability to void [63].
At a central level, decreases in regional cerebral blood flow measured by PET scanning was demonstrated in the cingulate gyrus, orbitofrontal cortex, midbrain and adjacent midline thalamus in chronically implanted patients with urge incontinence [72]. SNM appears to restore activity associated with brainstem auto regulation and attenuation of cingulate activity [73, 74], critical to bladder function.

Historically, the management of urinary incontinence and retention, with SNM has classically been with successful pre-test stage using percutaneous nerve evaluation before permanent implantation. Success rates with this method have been reported at 40 – 50% [67, 75] for the PNE and approximately 60% voided to completion with formal implant and a further 14% reported significant improvement at 18 months our results show that a two third of patients continue to void without catheterization at a mean follow up of 5 years [76] and 78% at a mean follow-up of 10 years [77]. The relatively low success rate of the PNE and single stage implant has led to the development of the staged implant, whereby the permanent 'tined' lead is inserted and a prolonged external stimulation period is assessed [78], if successful then the permanent IPG is implanted. Early reported results with this technique show 80% success rates [78, 79]. A pilot prospective randomised controlled trial comparing the 1-stage to the 2-staged shows a higher success rate for the staged operation. [80]. Results from our department are in line with these reports.

Our Department has previously reported on the traditional implantation technique that was used first at our unit using a one-stage procedure [62], preceded by a PNE. This took place until August 2004, until the author took over the programme for the hospital. The PNE was a way of evaluating the success of the final implant without the cost and trauma of the final implant and surgery respectively. The testing wire would remain in place for up to 7 days and if patients reported at least a 50% improvement in their symptoms and their bladder diary confirmed this, they would go on to have a permanent lead and stimulator.

The disadvantage of the PNE was the rather variable success rate of 24-75% [67, 78, 80-85]. Although these patients were labelled as non-responders, the real reason for a

proportion was dislodgement of the testing wire from the original optimum position close to the sacral branches of the pelvic plexus or pudendal nerve. Sacral radiographs often demonstrated that the wire had moved or was out of the foramen completely.

In previous reports of this technique there were several drawbacks noted, as up to 40% of patients who responded to the temporary PNE, did not void on insertion of the permanent electrode. A possible reason for this is that the site of permanent electrode implantation may have differed from that of the “successful“ PNE electrode [86]. Conversely the PNE temporary electrode may not be optimally placed leading to failure and patients not proceeding to permanent implantation [82]. In 1997, Janknegt et al., suggested the implantation of the permanent standard electrode in patients with a strong suggestive history, in whom the PNE failed [82]. In 2000 the two-stage percutaneous minimally invasive technique came into its own with the emergence of the self-securing tined electrode [67, 82]. This has a longer “test phase” to evaluate the procedure. Early data suggested that this has a higher success rate than the one-stage procedure of up to 80% [79, 80] and this has been our adopted method since 2004.

Using a percutaneous technique, fluoroscopic guidance, and local or general anaesthesia a permanent electrode is implanted as the first stage, and connected to a temporary external battery. If the first stage fails, the electrode can be removed. It is the authors’ belief that the two-stage technique overcomes problems with PNE lead migration. It helps clinicians decide which patients should go on to have a permanent battery. The average battery life with Interstim® and Interstim II® is around 8 and 5 years, respectively, but this varies with the settings used [87].

SNM is not without its complications and need for revision surgery. Therefore, it is important that patients are counselled regarding failure of the procedure (25%), the significant revision rate (30-50%), and the risk of box site pain, sciatica and nerve injury (very low). At 10 year follow-up at the National Hospital for Neurology and Neurosurgery, 78% of the patients who previously had significant impairment or inability to void, were able to void [69, 77]. Despite proven efficacy the procedure is not without a significant complication rate both at our and other centres using the same technique [62, 88]. This includes lead migration, pain at the Implantable Pulse Generator (IPG) site, leg pain, infection and failure of the device over time. This finding is confirmed by other studies which reported an incidence of 11% in lead migration [15] and 20% in lead breakages[86, 87]. Siegel et al. summarised their adverse events in the 219 patients who underwent implantation of the Interstim® IPG and the most common complaint was pain at the IPG site in 15.3% of patients [85]. The surgical revision

rate was 33%. Everaert et al. reported a 34% device related pain rate, with a 23% surgical revision rate [89]. Grunewald et al. reported a revision rate of 30% over 4 years. Lead migration was noted as 5.4% and IPG site pain as 8.1% [90]. Recently authors have reported much higher long term revision rates with 54% [62], 48.3% [87] and 43.9% [91] excluding normal battery changes. Similar results were obtained in a worldwide SNM clinical study in voiding dysfunction, carried out by Van Kerrebrock (2007) and colleagues [92].

The most important determinant of success, in women with chronic urinary retention or other pelvic floor symptoms (including pelvic pain syndromes, sexual dysfunction and bowel dysfunction) is the careful selection of the patient. This includes a urological and gynaecological history, pelvic examination to rule out surgical correctable causes and urine assessment to rule out infection and haematuria. We advocate the use of frequency-volume charts, urodynamic evaluation where indicated, post void residuals if they are able to void at all and quality of life questionnaires to qualify the degree of improvement before and after the procedure.

In the last decade there has been a plethora of innovative neuromodulation devices for treatment of lower urinary tract symptoms and pelvic floor dysfunction, though sacral neuromodulation remains the most widely used form of peripheral neuromodulation. In this workshop, a review of the role of pudendal neuromodulation, percutaneous tibial nerve stimulation and sacral dermal neuromodulation devices will also be considered. Their place in an algorithm of bladder and pelvic floor management will be devised.

Take Home Message

-Neurological basis of bladder and pelvic floor dysfunction is essential to all practitioners
-In neurological patients, practitioners should investigate all aspects of bladder and pelvic floor dysfunction
-Different therapeutic options should be made available and discussed with all patients

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Neurology of the bladder and pelvic floor

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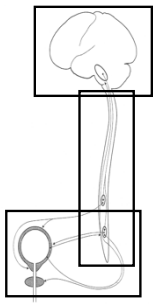
Universität Zürich

Social impact of micturition

„Manneken Pis“ (Brussels)

Multilevel process

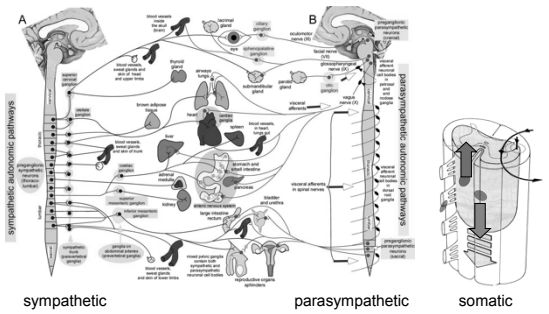


cerebral

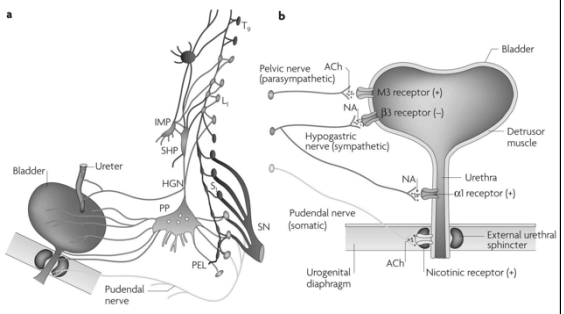
spinal

peripheral

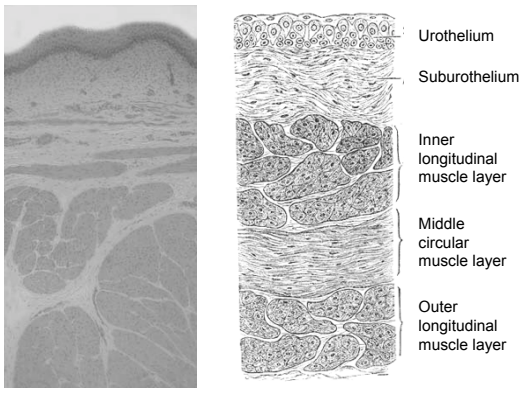
Afferent and efferent nerve fibers

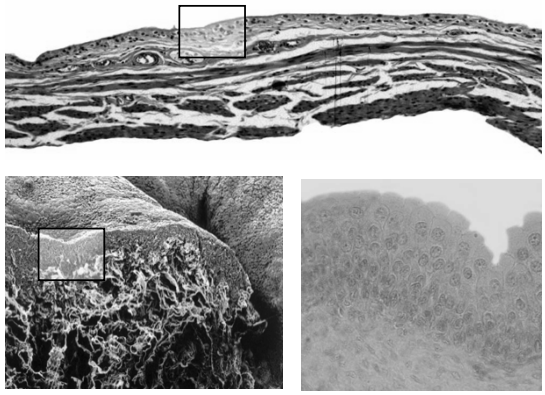


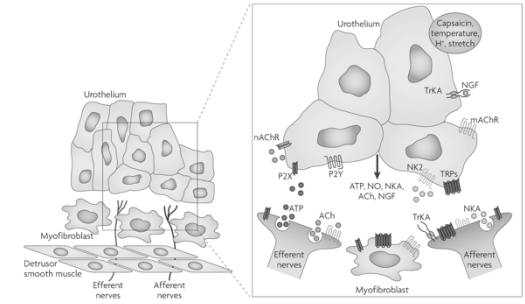
sympathetic parasympathetic somatic



Fowler CJ et al., Nat Rev Neurosci 2008







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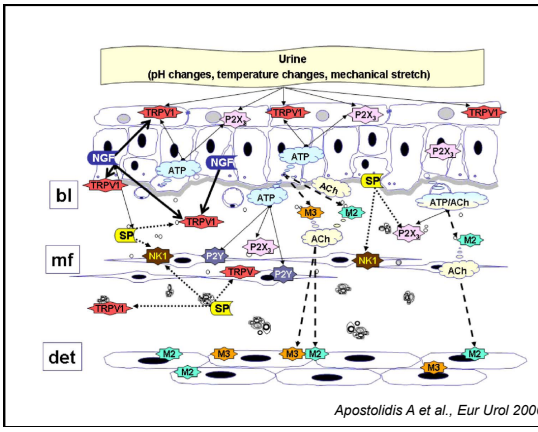
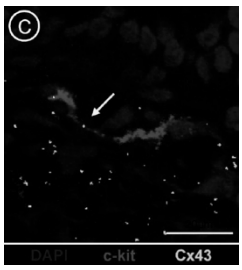
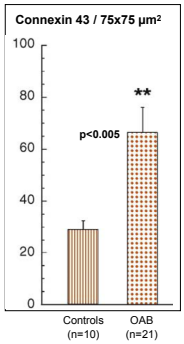


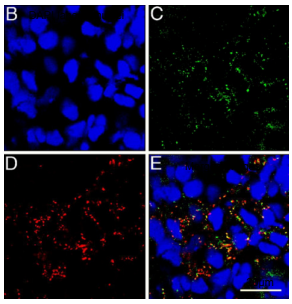
Apostolidis A et al., Eur Urol 2006

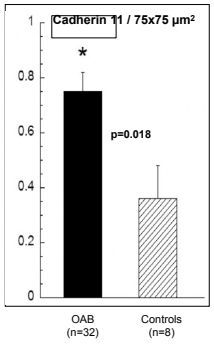




Suburothelium: „gap junction“ protein connexin 43 ↑

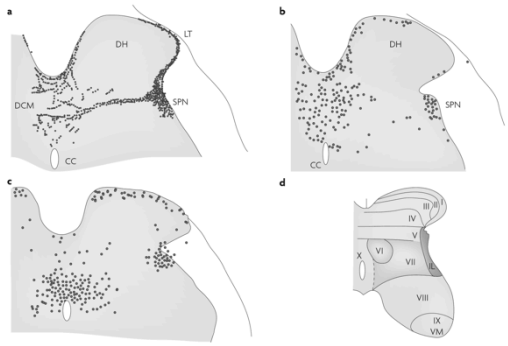
Roosen A et al., Eur Urol 2009



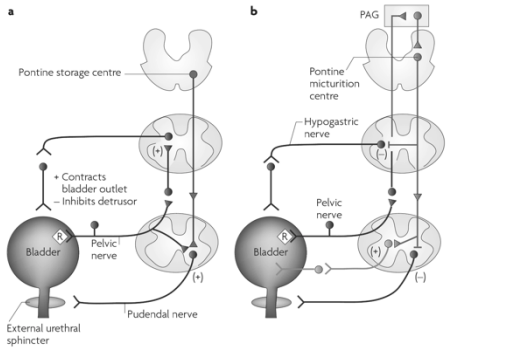


Suburothelium: „adherens junction“ protein cadherin 11 ↑

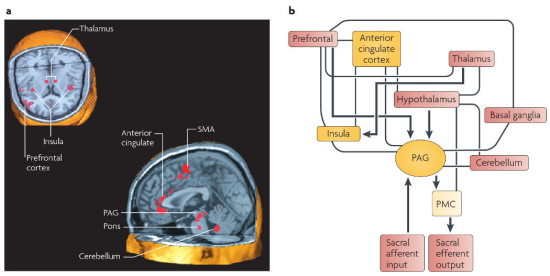
Roosen A et al., J Urol 2009



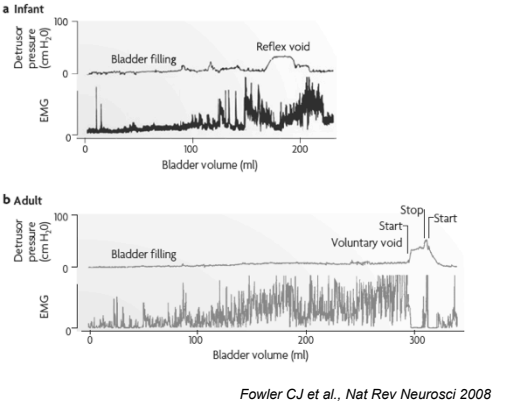
Fowler CJ et al., Nat Rev Neurosci 2008



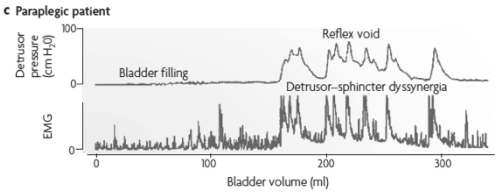
Fowler CJ et al., Nat Rev Neurosci 2008



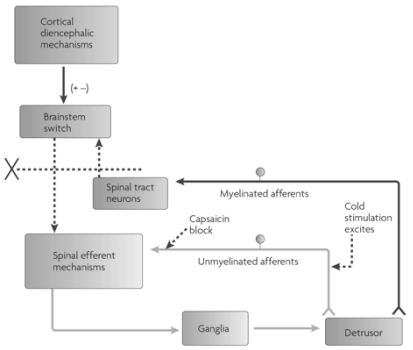
Kavia R et al., J Comp Neurol 2005
Dasgupta R et al., BJU International 2007



Fowler CJ et al., Nat Rev Neurosci 2008



Fowler CJ et al., Nat Rev Neurosci 2008

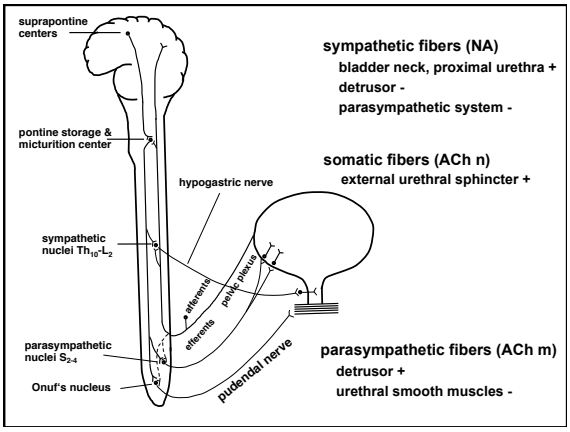


Fowler CJ et al., Nat Rev Neurosci 2008

Conclusions

Complex multilevel process

- Interaction urothelium, suburothelium and detrusor
- Spinal interneuronal pathways
- Specific cortical and subcortical regions


suprapontine centers
pontine storage & micturition center
hypogastric nerve
sympathetic nuclei Th_{10}-L_2
afferents
pelvic plexus
efferents
parasympathetic nuclei S_{2-4}
Onuf's nucleus
pudendal nerve
sympathetic fibers (NA)
bladder neck, proximal urethra +
detrusor -
parasympathetic system -
somatic fibers (ACh n)
external urethral sphincter +
parasympathetic fibers (ACh m)
detrusor +
urethral smooth muscles -